Neuropsychiatric Disease and Treatment

Treatment of refractory complex partial seizures: role of vigabatrin

Abstract: Vigabatrin (VGB) is an antiepileptic drug that was designed to inhibit GABA-transaminase, and increase levels of γ-amino-butyric acid (GABA), a major inhibitory neurotransmitter in the brain. VGB has demonstrated efficacy as an adjunctive antiepileptic drug for refractory complex partial seizures (CPS) and for infantile spasms (IS). This review focuses on its use for complex partial seizures. Although VGB is well tolerated, there have been significant safety concerns about intramyelinic edema and visual field defects. VGB is associated with a risk of developing bilateral concentric visual field defects. Therefore, the use of VGB for complex partial seizures should be limited to those patients with seizures refractory to other treatments. Patients must have baseline and follow-up monitoring of visual fields, early assessment of its efficacy, and ongoing evaluation of the benefits and risks of VGB therapy.

Keywords: vigabatrin, epilepsy, complex partial seizures, review

Introduction

The discovery of γ-aminobutyric acid (GABA) as the first major inhibitory neurotransmitter, and a program exploring the use of enzyme inhibition as a therapeutic tool provided the basis for the conception of vigabatrin (VGB). VGB was first approved in the United Kingdom in 1989, and is used in over 50 countries as an adjunctive therapy of adult patients with refractory complex partial seizures (CPS), and as a treatment for patients with infantile spasms (IS). This review focuses on its use for CPS. VGB has not been available in the United States, due to concerns about its safety. After further analysis of data regarding adverse effects and safety, clinical monitoring guidelines are being developed to reduce the potential risks associated with its use in patients with these severe epileptic conditions.

Pharmacology

The VGB molecule, a structural analog of GABA, was designed to have enzyme-activated highly specific activity as an irreversible inhibitor of GABA-transaminase. Vigabatrin (4-amino-5-hexenoic acid, or γ-vinyl GABA) was first synthesized in 1977 as a selective irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T). By inhibiting GABA-T, the enzyme responsible for the catabolism of GABA, VGB increases whole brain levels of GABA, leading to a reduction in seizure activity.

The molecular structure of VGB is shown in Figure 1. VGB is a racemic compound and its [S]-enantiomer is pharmacologically active. When administered orally, VGB is rapidly and near-completely absorbed and has dose-proportional and linear...
pharmacokinetics. VGB is completely absorbed following oral administration and can be given without regard to meals.\(^4\) After administration, peak VGB concentration occurs within 2 hours.\(^5\) It is widely distributed with a volume of distribution steady-state of 1.1 L/kg and does not bind to plasma proteins. VGB is not metabolized and is eliminated unchanged by renal excretion.\(^6\)

The \(T_{1/2}\) of VGB is approximately 5 to 7 hours; however plasma levels are not correlated with clinical effect.\(^7\) A study of patients with epilepsy given single oral dose of VGB found that peak levels were achieved in less than 1 hour in the serum, and 6 hours in the CSF. GABA levels remained elevated in the CSF for over 1 week.\(^8\) The duration of the clinical effect of VGB is thought to be dependent on the rate of GABA-T resynthesis rather than on the plasma concentration of VGB. The rate of recovery of GABA-T is 5 days.\(^1\)

*In vitro* metabolism studies show that there is a low potential for drug-drug interactions with VGB due to enzyme induction of CYP2B6 or CYP3A4.\(^9\) However, in some clinical studies, VGB was associated with modest decreases in plasma phenytoin levels.\(^10,11\) The cause of these findings is unclear, as VGB is not protein bound, and is not metabolized.\(^12\) A mild increase in carbamazepine (CBZ) levels in patients receiving adjunctive VGB has also been reported.\(^13\) These findings suggest that levels of concomitant antiepileptic drugs should be monitored, but dose adjustment is usually unnecessary.

**Vigabatrin and infantile spasms**

Although VGB plays an important role in the treatment of IS, a comprehensive review of its efficacy for spasms is beyond the scope of this article. In brief, investigators have reported cessation of infantile spasms in 16% to 76% of patients with IS.\(^14,15\) Studies have been complicated by methodological issues, including the ethics of administering a placebo, and the challenge of accurately documenting outcomes in a condition that causes numerous brief spasms daily. Evidence suggests that hormonal treatment achieves spasm resolution more quickly and in more infants than VGB treatment.\(^16\) However, VGB may be the treatment of choice for IS due to tuberous sclerosis.\(^16\) A meta-analysis of studies assessing the efficacy of VGB for IS found that 95% of patients with tuberous sclerosis achieved freedom from spasms, while the rate was 54% for patients without tuberous sclerosis.\(^17\) A 2009 long-term follow-up study comparing VGB and ACTH treatment in 28 patients with idiopathic West Syndrome found no significant difference in short-term seizure response (80 and 88%, respectively), although ACTH was associated with better long-term cognitive outcome.\(^18\)

**Efficacy of vigabatrin for refractory complex partial seizures**

A number of well designed trials have found VGB effective as adjunctive therapy in patients with refractory complex partial seizures. Responder rates (\(\geq 50\%\) seizure reduction) have varied according to study design and VGB dose. A review of double-blind, placebo-controlled studies of adjunctive therapy with newer antiepileptic drugs reported that the overall responder rate for VGB 3 g daily was 44.2%, and the placebo responder rate was 13.8%.\(^19\)

In the 1980s, several double-blind, placebo-controlled crossover design studies of VGB as adjunctive treatment for partial seizures were performed, demonstrating responder rates ranging from 33% to 67% with doses of 2 to 3 g daily.\(^11,20-23\) The variability of responder rates is likely due several factors: the small number of patients analyzed, and the inclusion, in some studies, of generalized seizures.\(^11,23\) A larger, similarly designed 1996 Australian study of 97 patients with uncontrolled CPS found a responder rate of 42%.\(^24\)

A single-blind, placebo-controlled, multicenter trial of VGB was carried out in 101 patients with epilepsy, most of whom had refractory partial seizures. The inclusion of patients with other types of epilepsy may have contributed to the 11% drop-out rate, which was primarily due to increased seizure frequency. Among those completing the trial, the median number of monthly seizures decreased from 16 during the placebo phase to 5 during the final 8 weeks of treatment. A greater than 50% reduction in seizure frequency (compared to placebo) was observed in 60 patients.\(^25\)

A Canadian multicenter, double-blind, placebo-controlled parallel group trial of VGB in patients with refractory complex partial seizures and/or partial seizures with secondary generalization included 111 patients. The responder rate was 48% for VGB in doses up to 4 g daily, and 26% for placebo.\(^26\)
Two large trials of VGB for refractory complex partial seizures have been carried out in the US. The studies enrolled patients 18 to 60 years old, with an average 22-year history of epilepsy. Patients were taking 1 or 2 concomitant antiepileptic drugs (AEDs) at the time of entry into the studies. In both trials, a parallel group design was used, and the primary endpoint for efficacy was change in median monthly seizure frequency, compared to baseline, during the final 8 weeks of the study.

The study by French et al analyzed 182 patients taking either adjunctive VGB 3 g daily or placebo. VGB significantly decreased baseline monthly seizure frequency (~3.0) compared with placebo (~0.8), and 5.4% of the VGB patients became seizure free, while none of the placebo-treated patients achieved seizure freedom. The responder rate (50% reduction from baseline seizure frequency) was 43% for VGB and 19% for placebo. Statistically significant seizure reduction occurred early, after 2 weeks of VGB therapy, and was maintained during the 16-week treatment phase.27

A second US placebo-controlled, randomized, double-blind, multicenter study examined the efficacy and safety of 3 daily doses of VGB (1, 3, or 6 g) as add-on therapy in 174 patients with previously uncontrolled complex partial seizures. The responder rates were 7% for placebo and 24%, 51%, and 54% for patients taking daily VGB doses of 1, 3, and 6 g, respectively. Seizure freedom occurred in 9.5% of those taking 3 g daily, 12.2% of those taking 6 g daily, and none of those taking 1 g daily or placebo. As in the earlier study, seizure reduction was evident after 2 weeks of therapy (at the 3 and 6 g daily doses), and was maintained during the remainder of the study. There was no statistically significant difference in efficacy between the 3 and 6 g regimens.28

Adjunctive VGB therapy is effective for children with partial seizures. A prospective study including 178 patients with refractory partial seizures, aged 1 week to 19 years, found a 70% responder rate, and a 30% seizure freedom rate. Those with tuberous sclerosis had a particularly robust responder rate of 85%.29 These responder rates are higher than the rates reported for adults. The authors attribute the high efficacy rate to the fact that infants made up 22% of their study population, and infants responded better than older children to VGB. However, the inclusion of single-blind and open-label cohorts may also have introduced bias in favor of VGB treatment. A recent retrospective study reported a 34% responder rate in 59 infants and children with partial seizures, including 17% who became seizure free on VGB.30

To summarize, VGB has demonstrated significant efficacy as adjunctive therapy for patients with poorly controlled partial epilepsy, refractory to other antiepileptic drugs. Differences in inclusion criteria (especially type of epilepsy), VGB dosing, study population size and characteristics, and study design contribute to the variability of the reported response rates (approximately 40% to 60%). A meta-analysis of key clinical trials for 5 newer AEDs found that VGB had the most favorable improvement rates (responder rate minus placebo response) at recommended doses.31 Thus, adjunctive treatment with VGB is an appropriate consideration for patients who have failed treatment with available AEDs, have poor quality of life due to frequent complex partial seizures, and will comply with monitoring of for adverse effects. The potential for seizure reduction must be weighed against safety risks, which will be reviewed below.

Vigabatrin monotherapy studies

Several studies have evaluated vigabatrin as monotherapy, compared with carbamazepine (CBZ). The results suggest that VGB is the less effective, but better tolerated, of the 2 drugs. An open-label, randomized controlled study evaluated the efficacy, safety and cognitive effects of initial VGB monotherapy compared to initial CBZ monotherapy in patients with newly diagnosed epilepsy. A total of 100 patients, aged 15 to 64 years, with partial seizures and/or generalized tonic-clonic seizures were randomized to receive either VGB (mean dose 50 mg/kg), or CBZ (titrated to plasma concentrations of 35 μmol/L) for 1 year. The primary outcome measure was the proportion of patients continuing successful treatment, and was 60% for both drugs, but this number reflects a broad definition of treatment success, which included “acceptable seizure control” in addition to seizure freedom. It is debatable whether the definition of acceptable seizure control (1 to 4 partial seizures and no more than 1 generalized seizure during a treatment period) is appropriate for patients with newly diagnosed epilepsy. Seizure freedom rates significantly differed between the groups: 52% for the CBZ group, and 32% for the VGB group. Although VGB had to be discontinued in some patients due to lack of efficacy, none discontinued due to adverse effects. In contrast, 24% of the CBZ group discontinued treatment due to adverse effects, primarily rash.31

Similar findings of relatively lower efficacy but better tolerability of VGB occurred in a randomized crossover study comparing CBZ and VGB in 51 patients with newly
diagnosed partial epilepsy. In this study, patients started on either 200 mg daily of CBZ or 1 g daily of VGB, and the doses were increased weekly until seizures ceased or intolerable side effects occurred. Seizure-free rates were 56% and 46% for CBZ and VGB respectively. Those patients with persistent seizures or intolerable side effects entered the cross-over phase, and received the other drug. Of the crossover patients, 43% receiving CBZ and 45% receiving VGB achieved seizure freedom. Considering both phases together, 51% of CBZ patients and 46% of VGB patients had seizure freedom and acceptable tolerance. Differences in efficacy were not statistically significant. Side effects were more frequent in the CBZ group (41%) compared with the VGB group (22%), but this difference was not statistically significant. The most frequent complaint was drowsiness, and fewer side effects occurred with VGB.

The largest monotherapy study involved 459 patients, aged 12 to 65 years, with previously untreated newly diagnosed partial seizures, randomized to monotherapy with either CBZ 600 mg daily or VGB 2 g daily. Patients had had at least 2 seizures in the previous year, including simple or complex partial seizures, with or without secondary generalization. The primary outcome was time to withdrawal from drug, a measure that encompasses efficacy and tolerability, and the CBZ and VGB groups did not significantly differ on this measure. Secondary outcomes included additional efficacy and tolerability parameters. Efficacy outcomes favored CBZ, with a significant difference in time to first seizure. At 1 year, 58% of CBZ-treated patients and 38% of VGB-treated patients remained seizure-free. VGB was better tolerated than CBZ, with significantly fewer VG patients withdrawing due to adverse effects (19% VGB vs 27% CBZ at 1 year). Patients reported drowsiness, fatigue, headache, and dizziness with each of the drugs. VGB was more frequently associated with weight gain and psychiatric symptoms, most commonly depression.

The results of these monotherapy trials consistently demonstrate that, in terms of efficacy, VGB is inferior to CBZ in patients with newly diagnosed partial onset epilepsy. VGB is not recommended for use as monotherapy in this clinical setting.

Seizure type

Limited data suggest that VGB is more effective for CPS than for generalized seizures. In general, few patients with primary generalized epilepsy or symptomatic generalized epilepsies were included in studies, and analysis has been hampered by variability in the diagnostic labels used by various authors. A review of 487 patients treated with VGB from published clinical trials included 52 patients with generalized seizures, including tonic-clonic, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, Ramsay-Hunt syndrome, absence, myoclonic seizures, symptomatic or secondary generalized epilepsies, and generalized seizures of unspecified type. The responder rate (at least a 50% decrease in seizure frequency) was 21% for these patients, while 46% were unchanged, and 25% were worse. The authors note that those with secondary generalized epilepsy had the worst response. In comparison, the VGB responder rate for patients from the same studies with CPS, with or without secondary generalization, was 49%.

Long-term follow-up

Several studies examining long-term follow-up have found that those patients whose seizures improved during initial treatment with VGB continued to show significant benefit 1–5 years later. Two small case series following VGB-treated refractory epilepsy patients for 6 to 10 years suggest that epilepsy may improve with continued VGB treatment, with some patients becoming seizure free over time.

Tolerability of vigabatrin

In general, VGB is well tolerated, with side effects that are frequently seen in the setting of AED therapy. When data were pooled from controlled trials in epilepsy patients, excluding those with IS, there were 588 patients on VGB and 373 taking placebo. The most frequent side effects were fatigue (VGB 22.3%, placebo 15.3%), dizziness (VGB 18.9%, placebo 15.6%), somnolence (VGB 16.3%, placebo 9.9%), and increased weight (VGB 11.1%, placebo 7.2%). Among these patients, 15% of those treated with VGB discontinued their participation in a study due to an adverse event, compared with 4.6% of the patients receiving placebo. The most common symptoms leading to discontinuation in the VGB treatment group were depression (VGB 1.7%, placebo 0.5%), convulsion (VGB 1.2%, placebo 0.5%), disturbance in attention (VGB 1.0%, placebo 0.5%), headache (VGB 1%, placebo 0.5%), and agitation (VGB 1.0%, placebo 0%).

Weight gain occurs more frequently in epilepsy patients treated with VGB, compared with placebo. In a monotherapy study, 11% of VGB patients gained weight, compared with 5% of those treated with CBZ. The degree of weight gain is variable, averaging 3.7 kg ± 0.2 kg in a long-term study of adjunctive treatment with VGB.
Another long-term follow-up study of 25 VGB responders found increases of 5–16% of initial body weight in 10 of the patients. Weight gain in these patients tended to occur after 3 to 6 months on VGB, and plateaued within several months.40

Cognitive and psychiatric side effects
Cognitive side effects are an important concern of patients with refractory CPS, and VGB has little effect on cognitive function.31,41–45 Although participants in one study reported sedation early in the course of treatment, the VGB responders showed significant improvement in composite scales of psychomotor function, memory, and self-rating.42 A battery of 8 standardized cognitive tests found a significant difference between the VGB and placebo groups only on the Digit Cancellation Test. Scores on this test decreased with increasing dose of VGB.44 A randomized, placebo-controlled, parallel-group study of VGB adjunctive therapy in 45 patients found a small but statistically significant reduction in motor speed, and a modest impairment of performance on a visual memory task.45

The potential for psychiatric side effects with VGB treatment has been under scrutiny since an early report of 14 cases of psychosis among 210 patients treated with VGB.46 Further studies have found a lower incidence of these symptoms. A 1996 literature review of controlled trials reported an incidence of severe abnormal behavior in 3.4% of adults treated with VGB.47 Pooled data from controlled studies of epilepsy patients, excluding those with IS, indicate that 7.8% of those on VGB had depression, and 5.4% reported confusional state, compared with 4.6% and 1.6%, respectively, in placebo-treated patients.48 A meta-analysis of data from placebo-controlled trials of adjunctive therapy with VGB found that the incidence of psychotic events with VGB was 2.5%, vs 0.3% with placebo.49 In smaller monotherapy trials, psychosis was not reported.51,52 In a larger monotherapy trial, 25% of patients taking VGB had psychiatric side effects, described as agitation, depression, insomnia, or “other,” compared with 15% of those taking CBZ.33

VGB is one of several antiepileptic drugs associated with depression.49 French et al reported depression in 12% of patients titrated to 3 g VGB daily, compared with 3% of patients receiving placebo.50 These findings are comparable to the results of a meta-analysis, which showed an overall incidence of depression of 12.1% in patients treated adjunctively with VGB, compared to 3.5% with placebo.48 The incidence of depression is lower, about 6%, with VGB monotherapy.35 Depression in the setting of VGB treatment is typically mild. In general, psychiatric side effects decrease with dose reduction or slow taper of VGB, and typically reverse with discontinuation of VGB.14,48

Safety issues
In addition to the side effects reported by patients, there are two safety issues that have been extensively investigated: intramyelinic edema (IME) and visual field defects.

Intramyelinic edema
IME was initially reported in rodents and dogs treated with VGB.50 In rats, myelin microvacuolation leading to IME was localized to the hypothalamus, fornix columns, and cerebellar white matter, while in dogs it was found in the hypothalamus, fornix columns, optic tract and chiasm.51 In another study, VGB caused dose- and time-dependent microvacuolation within white matter tracts of the cerebellum, reticular formation and thalamus in rodents, and the fornix and anterior commissure in dogs.52 On electron microscopy, the microvacuolation was caused by separation of the outer lamellar sheaths of myelinated fibers and has been termed IME. The edema developed over a period of several weeks, after which a relative plateau was reached. It was reversible in both rats and dogs 12 to 16 weeks after stopping VGB. Dogs did not have any residual pathology after recovery, but rodents retained swollen axons and foci of microscopic mineralization within the cerebellum after recovery. Monkeys were studied, but did not demonstrate any conclusive pathological changes.52 Because the inactive R-enantiomer of VGB is not associated with IME, while the active S form is, IME is thought to be related to higher levels of brain GABA.6,52

Human trials of VGB were suspended in 1983 in the US due to the recognition of IME in rodents and dogs. Evoked potential studies and MRI proved to be sensitive non-invasive techniques to diagnose IME in these animals, and to confirm its absence in humans and other primates. Clinical trials were allowed to resume in 1990 after review of additional data.6 Autopsy and surgical brain specimens failed to show evidence of IME in children or adults with complex partial seizures.53 MRI was also normal in humans treated with VGB in doses from 1 to 6 g per day for 3 months to 12 years. A review of data from 350,000 patient-years of VGB exposure found no definite case of VGB-induced IME.54

The assumption that IME is a species-specific adverse effect of VGB not affecting humans was called into question in 2006, when MRI signal changes consistent with IME were reported in infants with IS, treated with VGB.55 A follow-up study reported MRI T2 hyperintensities in the basal ganglia,
thalami, anterior commissure and corpus callosum in 7 out of 22 patients, ranging in age from 3 months to 18 years, all of whom were treated for IS.\textsuperscript{55} In all of the patients, the T2 hyperintensities resolved with discontinuation of the medication.

Subsequent studies have confirmed MRI signal changes associated with VGB in infants.\textsuperscript{56,57} Wheless et al retrospectively reviewed MRI findings in VGB-treated patients, including 205 infants with IS, and a group of 668 patients (children over the age of 2 years, and adults) with refractory CPS.\textsuperscript{56} A statistically significant increase of pre-specified MRI abnormalities occurred only in the infants with IS treated with VGB. The prevalence of MRI abnormalities was 22\% in the VGB-treated infants, compared with 4\% for VGB-naïve infants, while no statistically significant difference occurred in those treated for CPS.\textsuperscript{56} VGB-associated MRI changes in infants may not be limited to those with IS; they have also been described in a small number of infants with focal epilepsy and epileptic encephalopathy.\textsuperscript{57}

MRI abnormalities associated with VGB in infants have typical characteristics. They are best seen on T$_2$-weighted, FLAIR and diffusion-weighted images, and occur predominantly in the basal ganglia, thalamus, brainstem, or cerebellum.\textsuperscript{56} They tend to peak after 3 to 6 months of exposure to VGB and most resolve, even with continued use of VGB.\textsuperscript{56,57} Although VGB is associated with a risk of MRI abnormalities in infants, there is no evidence for MRI changes due to VGB in children or adults with refractory CPS.\textsuperscript{56} Investigators have hypothesized that developmental changes in myelination in infants, or an underlying metabolic condition, may predispose infants, but not older individuals, to VGB-induced MRI changes.\textsuperscript{56}

Visual field defect
The most significant and unique VGB-specific side effect is a peripheral visual field defect, occurring in one third or more of patients treated with VGB.\textsuperscript{58} Rare sporadic visual field defects were reported during VGB development. In 1997, Eke et al published 3 case reports describing severe persistent peripheral visual field loss in patients who had been on VGB for over 2 years.\textsuperscript{59} The patients presented with “tunnel vision” and one presented after noticing increased frequency of bumping into objects after 2 to 3 years on VGB. Eke’s report was followed by several case series documenting visual field defects in the setting of VGB adjunctive therapy. A troubling finding was that visual field defects frequently were asymptomatic. Patients did not recognize that their visual fields were impaired. Even patients with severe visual impairments sometimes attributed the difficulties that they experienced to clumsiness or drowsiness, and the nature of the problem was not clarified until visual field testing was performed.\textsuperscript{58} These difficulties in reporting and diagnosing visual field defects led to delayed recognition of this problem as an adverse effect of VGB, and under-estimation of the risk in early studies. The median time to onset of the first observation of bilateral concentric peripheral field constriction in patients with CPS was over 4 years.\textsuperscript{6}

The peripheral visual field defect typically begins as a bilateral nasal defect, and progresses to bilateral concentric field constriction (see Figure 2). Initially, the visual defect is asymptomatic and is detected only by static or kinetic

\textbf{Figure 2} Humphrey visual field map of a patient treated with vigabatrin (VGB). While the visual field defect in patients treated with VGB is typically similar in both eyes, in this patient, the right eye has restriction of the nasal field, while the left eye is more severely affected, demonstrating concentric restriction.
perimetry or electroretinogram (ERG). The earliest detectable visual field deficit is usually peripheral field depressions that later increase centripetally and rarely progress centrally.\textsuperscript{60} It is hypothesized that patients do not notice the decreased peripheral vision loss early in the course of treatment because the initial peripheral vision loss occurs nasally and the binocularity of human vision compensates for nasal visual field loss. Symptomatic patients tend to have bilateral concentric field constriction, with involvement of their temporal visual fields, which are more likely to affect daily function since there is no visual field overlap temporally.\textsuperscript{6} VGB exposure has not been shown to cause significant problems with central visual acuity.

**Pathophysiology of VGB-associated visual field defect**

Although the pathophysiology of VGB-induced visual field defects is not entirely clear, animal studies have characterized retinal changes. Albino rats demonstrate dose-dependent concentration of VGB in the outer retina and also demonstrate retinal degeneration.\textsuperscript{61} The retinal changes occur in the periphery and involve the outer nuclear layer, with displacement of the nuclei into the rod layer. VGB itself accumulates in the retina in significantly higher concentrations relative to other tissues, and is associated with accumulation of GABA in the retina.\textsuperscript{62} In the setting of VGB treatment, animal studies demonstrate decreased activity of glutamic acid decarboxylase and GABA transaminase activity, and accumulation of GABA in the retina. Wang et al hypothesize that VGB may be associated with impaired glutamate release, based on abnormal retinal synaptic plasticity seen on examination of retinal tissue of albino mice treated with VGB.\textsuperscript{63}

A recent study suggests that light exposure and taurine deficiency may contribute to retinal damage and peripheral field defects in the setting of VGB treatment.\textsuperscript{64} In this study, VGB-treated rats exposed to cycles of 12 hours of light and 12 hours of darkness exhibited more pronounced retinal lesions than those kept in darkness alone. It was also noted that taurine levels were 67% lower in VGB-treated animals compared with control animals, and taurine levels correlated with ERG amplitudes. Although dietary taurine supplementation did not reverse existing retinal changes, it reduced the development of retinal damage. The study suggests that, in rats, VGB induces a deficiency in taurine, resulting in retinal phototoxicity.\textsuperscript{64} To assess the potential relevance of these findings to humans, the authors retrospectively reviewed data for 6 VGB-treated infants with infantile spasms. Five of the infants had low or undetectable taurine levels, including one who had a normal level prior to VGB treatment.\textsuperscript{64}

**Risk factors for the development of visual field defects**

Visual field defects occur in a significant number of patients treated with VGB, but studies of the prevalence and risk factors for VGB-associated visual field defects have reported widely varying results due to a variety of factors. These include the retrospective nature of the studies, the small numbers of patients studied, the lack of patient symptoms, the long latency until the condition was recognized and characterized by clinicians, and the variety of visual testing techniques used.\textsuperscript{65} Reviewing 11 studies, Kalviainen et al\textsuperscript{19} found an overall prevalence of bilateral concentric visual field defects in 32% of 528 patients treated with VGB. In 22 studies reviewed by Kinirons et al\textsuperscript{66} peripheral visual field constriction occurred in 19% to 92% of adults with CPS treated with VGB, and up to 31% of infants with infantile spasms. In most of these studies, VGB was used as an adjunctive antiepileptic drug. VGB-associated visual field deficit has also been seen in patients treated with monotherapy. A study of newly diagnosed epilepsy patients who had been randomized to monotherapy with either VGB or CBZ, found that 41% of the 32 patients receiving VGB had visual field constriction, while none of the 18 patients receiving CBZ was affected.\textsuperscript{67}

It is unclear why some patients develop peripheral visual field defects on VGB and others do not. Studies suggest that males have twice the risk of developing a visual field defect from VGB compared to females.\textsuperscript{58,68–72} Smoking has also been reported as a risk factor.\textsuperscript{6,58} However, a cohort study of 93 patients did not identify increased risk due to these factors.\textsuperscript{73}

There are contradictory reports regarding the risk of visual field defect and its relationship to cumulative exposure to VGB, maximum dose, and duration of dose. Several studies did not find evidence that these parameters correlated with the development of visual field defects.\textsuperscript{58,68,71} However, a cohort study of the cumulative incidence of visual field defects and cumulative VGB dose in 291 patients found that the cumulative incidence of visual field defects rapidly increased within the first 2 kg of VGB intake, and stabilized after a total of 3 kg of VGB.\textsuperscript{69} Conway et al\textsuperscript{74} suggest that maximum daily VGB dose is a predictor for development of peripheral visual field defects, and not cumulative or duration of dose.\textsuperscript{74} Other studies have also suggested that degree or
duration of VGB exposure correlate with the development of peripheral visual field defects.60,75–80

Visual field defects in children
Although some studies have suggested that children treated with VGB are less likely than adults to develop visual field defects, a recent study found only a small difference between children 8 to 12 years of age and older study participants. The proportion of patients with visual field defects was 29% for those 8 to 12 years of age, and 33% for those over age 12. This difference was not statistically significant, possibly due to the small size of the comparison groups.55 The risk of VGB-associated visual field abnormalities may be lower in children who were treated with VGB in infancy, compared to those who received it later in childhood. Mild visual field loss was found in 1 of 16 children, aged 6 to 12 years, who had been treated with VGB during infancy for IS.81

Time course of visual field defect
Analyses of the time course of peripheral visual field defects with VGB suggest that it develops gradually. Ovation Pharmaceuticals reports that, in patients with CPS on VGB, the earliest documented peripheral visual defect occurred after 9 months of treatment in adults, and after 11 months in children.6 There is a case report of a visual field defect developing within 6 months of VGB treatment.82 After 5 years of VGB treatment, the risk of development of peripheral visual field defect decreases sharply.73

Although varying methods of testing and the variability of patient responses make it difficult to combine study results, on average the progression of the visual field defect is <2 degrees per year from the temporal visual field and <1 degree per year in the nasal field.6 Once the peripheral visual fields are affected, the defect is usually irreversible but does not worsen over time.70,83 In a study of 60 adults with CPS treated with VGB for up to 14 years, 40% had visual field defects. At follow-up, after an average of 15 months, there was no significant progression in patients who continued to take VGB and no recovery in those who had discontinued it. Ovation Pharmaceuticals reported 1 patient who had progression of his visual field defect 4 years after discontinuing VGB.6

Diagnostic testing of visual fields
Several options are available to test for visual field defects. The only method appropriate for testing infants, young children, and adults unable to cooperate with visual field testing is the ERG, during which an electrode is placed on the eye to monitor the response of the retina to flashes of light. Although the ERG is not a direct test of visual fields, widespread and multifocal ERG techniques are highly sensitive at detecting VGB-associated retinal pathology.84–86 Perimetry techniques require patient cooperation. Kinetic perimetry, of which the most commonly performed is Goldmann perimetry, consists of an examiner moving stimuli through the patient's peripheral visual field and mapping defects on a reference grid. Static perimetry uses automated visual field analyzers, such as the Humphrey visual field analyzer, to determine the threshold intensity that the patient can perceive at specific locations in the visual field. The patient's reaction is then measured and mapped to display the visual field. Routine visual evoked potentials (VEPs) are not useful for assessing retinal changes, but field-specific VEPs have identified VGB-induced retinal defects in children over 2 years of age.87

A “gold standard” test for identifying VGB-associated visual field defects has not been established. Thus the true sensitivities and specificities of various techniques in this
Clinical setting cannot be calculated. In one study, objective outer limit testing (a “bedside” method performed by an examiner with a flashlight) detected 83% of the visual field defects identified by Goldmann perimetry, while manual kinetic perimetry detected 93%, and high pass resolution perimetry (a computer-based central field test) had a sensitivity of 72%. In general, while ERG is the most specific test, both static and kinetic perimetry are believed to have adequate sensitivity to monitor peripheral vision with VGB. As our knowledge of the pathophysiology of the VGB field defect progresses, it is likely that the optimal strategy for visual testing will evolve.

A promising technique for identification of VGB-associated visual abnormalities involves imaging of the retinal nerve fiber layer. The characteristic pattern consists of thinning of the nasal quadrant but sparing of the temporal quadrant. This finding may precede visual field loss. A recent study that measured the thickness of the retinal nerve fiber layer using ocular coherence tomography found this pattern in all of the 11 patients with confirmed VGB-associated visual field deficits, as well as 4 of 15 VGB-treated patients who had normal fields. These findings suggest that nasal retinal nerve fiber layer attenuation is a promising biomarker for VGB toxicity, and may be valuable indicator for consideration of VGB withdrawal.

Recommendations for visual field monitoring

All patients with refractory CPS who are considering treatment with VGB should have a baseline visual field examination. VGB should not be used in those with restricted visual fields at baseline. VGB-treated adults should have a follow-up visual field examination every 6 months. Infants should be tested at 3-month intervals for the first 18 months of treatment, and then every 6 months. It has been well documented that response of CPS to VGB is evident by the 12th week of therapy, earlier than the reported onset of visual field defects. If substantial improvement in CPS has not been achieved by 12 weeks of VGB therapy, then the drug should be stopped in order to minimize the risk of developing a peripheral visual field defect. If VGB treatment is successful in treating refractory CPS, the risks and benefits at that point should be re-evaluated with the patient. Data suggest that after 5 years of VGB exposure, the risk of developing a peripheral visual field defect stabilizes and therefore less intensive monitoring may suffice at that point.

Conclusions and recommendations

Approximately 30% of patients with epilepsy have seizures that continue to occur despite pharmacologic treatment. Uncontrolled seizures can severely impair a patient’s quality of life, and may lead to seizure-related injuries or even sudden unexplained death in epilepsy. Improvement in seizure control in this population can positively affect prognosis and patient well-being.

The major benefit of VGB is that it has demonstrated efficacy in some patients whose seizures have been resistant to other drugs. A comparison of key clinical trials of newer antiepileptic drugs found a favorable efficacy and side effect profile for VGB in the adjunctive treatment of CPS. It has few cognitive side effects, and is generally well tolerated by patients.

These potential benefits must be balanced with the significant risk of developing a visual field defect, which develops in about one third of patients taking VGB. Because of this risk, VGB should be considered only as adjunctive therapy for those patients whose CPS have not responded to other treatments, and who are not appropriate candidates for other therapies, such as epilepsy surgery. Since the onset of visual field defects is usually asymptomatic, visual fields and/or ERG must be checked at baseline, and every 3–6 months during treatment, to monitor for the development of defects. General recommendations for patient selection and monitoring are listed in Table 1. A cautious strategy of targeted patient selection and careful monitoring for visual field defects should optimize the risk-benefit ratio of VGB in the clinical setting.

Disclosures

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References


