Vigabatrin

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INTRODUCTION

Vigabatrin (VGB) is a structural analog of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the mammalian brain. It was synthesized in 1974 as the first “designer” anticonvulsant drug with an intended and specific mechanism of action. It binds irreversibly to GABA transaminase (GABA-T), the enzyme that breaks down GABA. This action increases the brain levels of GABA, thus increasing inhibition in the brain and decreasing the likelihood of seizures.

VGB has been approved for treatment in nearly 50 countries worldwide and its release in the United States can be expected in the near future. VGB has been studied extensively in adults with complex partial epilepsy with the first reports dating to 1983. Pediatric studies were first reported in 1989. When VGB is approved, it is likely to play an important role in the treatment of pediatric epilepsy patients, especially in children with infantile spasms.

CHEMISTRY AND BIOCHEMICAL MECHANISM OF ACTION

The chemical structure of VGB is 4-amino-6-hexenoic acid (γ-vinyl GABA). It was designed specifically to achieve irreversible inhibition of GABA-T (51). The enzyme γ-aminobutyric acid α-oxoglutarate transaminase (GABA-transaminase, GABA-T, EC 2.6.1.19), present in neurons and glia, causes oxidative deamination of GABA to succinic semialdehyde. Unlike several other inhibitors of GABA-T which also display some activity against the enzyme responsible for the synthesis of GABA (glutamic acid decarboxylase; GAD), VGB is selective in its antagonism of GABA degradation (89). The structures of GABA and VGB are shown in Fig. 1. The obvious structural similarity is responsible for the ability of VGB to interact with GABA-T. The presence of the vinyl moiety renders
VGB to a mechanism-based suicide substrate which is covalently (and irreversibly) bound to the enzyme. Only new enzyme synthesis can restore GABA-T activity. Thus, even a single dose produces a lasting, dose-dependent inhibition of brain GABA-T in experimental animals, and elevated GABA levels are seen for at least 24 h (51). After a dose of 1500 mg/kg of VGB in mice, GABA levels increased to a maximum of 650% of control in 4 h (9). Levels of excitatory amino acids glutamate and aspartate reached a nadir of approximately 80% of control values in about the same time. More recently, noninvasive measurement of brain GABA levels in humans by the application of 1H magnetic resonance spectroscopy has permitted the demonstration of 2.5- to 3-fold elevations in GABA levels in the brains of epileptic patients treated with standard doses of VGB (61,73).

The compound possesses a chiral center and thus is commonly distributed as a racemic mixture of R(–) and S(+) enantiomers. Pharmacologic activity has been attributed only to the S(+) isomer (63). It was subsequently shown that only the S(+) isomer could be transported into neurons and also that neuronal uptake was much more efficient than glial uptake (90).

Vigabatrin has been in use in a large number of countries for several years but its approval in the U. S. is held back due to emerging concerns about symptomatic visual field defects and findings of retinal toxicity demonstrable by laboratory testing in asymptomatic individuals. This topic is discussed more fully under the section below on toxicology.

**PRECLINICAL PHARMACOLOGY**

The correlation between the activity of a compound against animal models of epilepsy and its effectiveness in human epilepsies is imperfect. Nevertheless, several models have been useful in providing us with a high degree of predictability about the spectrum of activity of new antiepileptic drugs (AEDs) against human epilepsies. The maximal electroshock (MES) test in rodents, and the threshold pentylenetetrazol (PTZ) test in mice have been carefully standardized (52). The MES model has served to identify AEDs that are functionally similar to phenytoin (PHT), and these compounds display in common the ability to inactivate voltage-dependent Na⁺ channels in a use-dependent fashion. Such
compounds suppress sustained repetitive firing in cultured neurons. Activity in this model seems highly predictive of the ability of those AEDs to protect against partial and secondarily generalized tonic-clonic seizures. The PTZ model has proven to be a good predictor of clinical efficacy against generalized spike-wave epilepsies of the absence type. Compounds that suppress $\text{Ca}^{2+}$ conductance across T-channels, such as ethosuximide (ESM) or valproic acid (VPA), as well as compounds that enhance GABA$_A$ receptor-mediated conductance of $\text{Cl}^-$, such as benzodiazepines, seem to be active in this model. Unfortunately, no accepted animal model exists for many of the catastrophic epilepsies of early childhood.

Models of Partial and Secondarily Generalized Seizures

Iadarola and Gale (50) reported a time-dependent reduction in the duration of the tonic hind-limb extension phase of MES seizures in rats treated with VGB. However, VGB was shown to be ineffective against MES seizures in mice (9,22,48). Thus the effect of VGB in rodents appears to be species-specific.

Models of Limbic Seizures

These models have been advanced as useful in the study of temporal lobe epilepsy in humans. The number of stimulations required for kindling development (total number of stimulations to class V seizures) in rats was approximately doubled by VGB (93); the afterdischarge duration was maximally suppressed at 24 h after the systemic administration of VGB. VGB was also capable of suppressing both generalized motor seizures and electrographic afterdischarges in previously fully kindled animals. In another model of limbic seizures, intranigral injections of VGB blocked the seizures caused by the systemic administration of pilocarpine (104).

Models of Primary Generalized Seizures

In the PTZ model, one that is commonly used to screen antiabsence agents, low doses of VGB decreased seizure intensity in mice, but higher doses were ineffective (86). In a study of the effect of high-dose VGB on PTZ seizures in male Sprague–Dawley rats, the prolongation of seizure duration resulted in status epilepticus (69). The spontaneous spike–wave activity seen in the Strasbourg rat, a genetically absence-prone subset of Wistar rats, was enhanced by VGB (109). The lethargic mouse (lh/lh) has been recently proposed as a genetic model of absence seizures with significantly improved predictive ability for the utility of test compounds in treating human absence epilepsy (49). This model, unlike the PTZ model, is able to correctly predict the antiabsence efficacy of lamotrigine. Proabsence effects of VGB were demonstrated in this model. Even though benzodiazepines, which are agonists at the GABA$_A$ receptor, are capable of abolishing these type of seizures, it is possible that the concomitant stimulation of GABA$_B$ receptors resulting from the increased concentrations of GABA due to administration of VGB
would have the opposite effect. These results would argue against therapy with VGB in the treatment of human absence epilepsy.

The genetically photosensitive baboon, *Papio papio*, has been used to study activity of anticonvulsants against myoclonic seizures. VGB was shown to be effective in abolishing photically induced myoclonus in this model (62).

While standardized animal models of the early childhood epilepsies are not available, Velíšek et al. (107) found that VGB did not prevent flurothyl-induced seizures in 9- and 15-d-old rat pups, while phenobarbital, a classic drug that acts by enhancing GABA<sub>A</sub>-mediated Cl⁻ currents, did. Such differences may reflect age-dependent maturational changes in GABA receptor subtypes.

**Neuroprotection in Experimental Status Epilepticus**

The neuroprotective and antiepileptogenic potential of VGB has been explored in animals. Halonen and colleagues showed that a dose of VGB (500 mg/kg i.p.) that had no effect on the generation and severity of status epilepticus by kainic acid nevertheless decreased the associated neuronal loss in the CA3a and CA1 fields of the rat hippocampus (44). Another study (116) had reported that pretreatment with VGB (500 mg/kg i.p.) resulted in the preservation of somatostatin-containing hilar cells in the sustained perforant path stimulation model, but it is not clear that adequate and self-sustaining seizures were elicited at this dose. A lower dose (100 mg/kg) did not show such neuroprotection in the same study. Nevertheless, a difference in neuroprotection in the perforant path stimulation model has been demonstrated between carbamazepine (CBZ) and VGB (76). Even though VGB and CBZ treatments had similar anticonvulsant efficacy during the perforant pathway stimulation, VGB, but not CBZ, decreased seizure-induced neuronal damage in the hippocampus. Such neuroprotection was not observed in the amygdala (76).

**BIOAVAILABILITY AND PHARMACOKINETICS**

Peak plasma concentrations were reached rapidly following oral ingestion of VGB by human volunteers (6,78). The area under the plasma concentration-time curves (AUC) was consistent with dose-linear pharmacokinetics and bioavailability (84). There was no effect of food on the absorption of VGB (30). While there is no intravenous preparation available for human consumption, the oral and intravenous routes produced similar AUCs in dogs, suggesting that oral VGB is almost completely absorbed (96). Detailed studies on the R(−) and S(+) enantiomers have not revealed any differences in the rates of absorption between the two enantiomers (43). The AUC for the S(+) enantiomer was slightly lower than that for the R(−), but this discrepancy is probably attributable to the removal of the biologically active S(+) form by covalent binding with GABA-T. The AUCs in different special populations (normal volunteers vs. epileptics, different ages) also did not differ sufficiently to be of clinical interest (78).

VGB is not protein-bound and its apparent volume of distribution after administration of the racemate has been estimated to be 0.8 L/kg, a value that is similar to total body
water (87). Concentrations of VGB in the cerebrospinal fluid (CSF) have been reported to be highly variable, but a clear relationship with dose was not established (8). It should be remembered that in theory the plasma or CSF concentrations of VGB are not particularly relevant to the control of seizures; rather, it may be expected to be the extent of covalent inactivation of GABA-T and the resulting increase in the concentrations of GABA. It is also reasonable to expect that once GABA-T is maximally inhibited, no further increases in brain GABA concentrations can be achieved by further increases in the dose of VGB. This has, indeed, been demonstrated with magnetic resonance spectroscopy in humans (74). Moreover, it is well known in clinical epileptology that brain GABA levels as estimated from cerebrospinal fluid (CSF) concentrations are difficult to correlate with seizure control. Specific regions of the brain have differential sensitivities to GABA for different types of seizures (31–34), and the relationship is not easily summarized within the scope of this review of a specific AED. Developmental specificity of these structures to manipulation of GABAergic tone has also been described (65,66,108).

VGB is not metabolized in the liver. It is excreted unchanged by the kidneys and its clearance of about 1.7 to 1.9 ml/min/kg is unaffected by dose or duration of treatment (43). Its elimination half-life is directly related to its renal clearance. The renal clearance of VGB is nonlinearly related to creatinine clearance (42). The elimination half-life is between 5 and 7 h.

Because VGB is not protein bound, nor is it metabolized by the hepatic microsomal system, one would not expect significant pharmacokinetic interactions with other drugs. Thus far, only one interaction of potential clinical significance with another AED has emerged. Rimmer and Richens initially documented a decrease in serum PHT concentrations from 59 ± 30 μmol/l during the placebo phase to 40 ± 43 μmol/l when VGB was added at a dose of 1.5 g twice daily (81). Brown and colleagues encountered a 20% decrease in serum PHT concentrations in their initial study (12) and later confirmed this finding (11). Rimmer and Richens also confirmed this interaction in a new study (82), which was designed to explore the mechanism of this unexpected interaction. They did not find a difference in the absorption, protein binding, or hepatic function as measured by antipyrine clearance.

**Clinical Studies of Efficacy in Humans**

**Studies in Adults**

Efficacy of VGB as an add-on AED in humans was first evaluated in two European placebo-controlled, single-blind pilot studies (40,88). Gram and colleagues achieved a 50% reduction in median seizure frequency when VGB was added during a treatment period lasting 12 weeks (40). Fifteen patients were enrolled in that study, of whom 13 had partial seizures with or without generalization while two were classified to have generalized seizures, including atypical absences. Schechter and associates reported that 60% of the patients (five with primary generalized seizures and five with partial seizures with or without generalization) attained complete seizure control; however, the active treatment period was shorter (4 weeks) (88).
Overall, six short-term, double-blind, placebo-controlled studies were completed in Europe between 1984 and 1987 with VGB as add-on therapy (Table 1). Doses ranged from 2 to 4 g and trial periods ranged from 7 to 12 weeks. The largest of these studies involved only 31 patients. The majority of patients had medically intractable complex partial seizures with or without secondary generalization, but a few patients with other seizure types had also been included. Meta-analysis of these six studies demonstrated that VGB produced a $>50\%$ decrease in seizure frequency in 46\% of the total of 98 adult patients having only partial seizures (68).

In a study of 20 patients who showed an initial response to VGB, Ring et al. (83) withdrew VGB and substituted it with a placebo in a randomly chosen group. Those who were retained on VGB continued to experience a 55\% reduction in seizures while those who were crossed over to the placebo sustained a 19\% increase in seizure frequency compared to their baseline prior to beginning VGB.

Only two significant U. S. studies have been reported as peer-reviewed papers. The first was a single-blind parallel study involving 89 patients with medically intractable complex partial seizures in which 51\% of the patients on VGB achieved a $\geq 50\%$ reduction in the frequency of seizures (12). Long-term follow-up of this cohort found that only 17 patients out of the 66 who had a favorable initial response to VGB dropped out either due to breakthrough seizure activity and/or side effects (11). Further longitudinal follow-up of this cohort contributed to the resumption of clinical trials of VGB that had been suspended in the U. S. due to concerns about white matter toxicity (see below under toxicity) (10). The other U. S. study involved a manufacturer-sponsored, placebo-controlled, double-blind, parallel design involving 182 patients (29). Of the patients who received VGB, 43\% enjoyed a 50\% or greater reduction in the frequency of their seizures while only 19\% of those on the placebo achieved a similar reduction.

Several other reports describe short- and/or long-term efficacy of VGB in patients with refractory epilepsy (7,21,23,54,57,72,79,99,100). Many of these reports have limitations based on the study design which permitted inclusion of patients with multiple seizure types (23,54,57,72,79,99,100). The significance of the impact of studying heterogeneous patient populations is highlighted by the analysis of Michelucci and Tassinari, who found that a majority of patients with primary generalized epilepsies (especially absences or myoclonic seizures) and secondary generalized epilepsy (such as Lennox-Gastaut syndrome) were either unchanged or worsened by VGB therapy (64). The poor clinical ef-

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ficiency of VGB in human absence epilepsy correlates well with data from animal models described in the section on preclinical pharmacology. Nevertheless, the important utility of the long-term studies is that they establish both sustained efficacy over time as well as tolerability. The former is of concern for an AED whose action is related to GABAergic mechanisms, since refractoriness to the effect of benzodiazepines develops rapidly in clinical practice.

**Pediatric Studies**

Vigabatrin may prove to be a particularly important addition to the list of AEDs available to pediatric epileptologists (92). Most AEDs are developed with adult patients in mind, and are targeted to counteract partial seizures with or without secondary generalization. Children have distinctive and development-specific epilepsy syndromes and the response of their seizure disorders to these AEDs is often unpredictable. For instance, AEDs like PHT and CBZ have no demonstrated efficacy against febrile convulsions in children who respond to barbiturates, benzodiazepines, or VPA. One of the most serious epileptic syndromes of infancy, infantile spasms (IS, also known as West syndrome), is usually refractory to traditional AEDs and the treatment of choice in the U. S. has relied upon corticosteroids or adrenocorticotropic hormone (ACTH). These approaches carry a substantial risk for severe adverse reactions and morbidity. The demonstration of the efficacy of VGB in IS is largely responsible for the enthusiasm this AED has generated among pediatric epileptologists.

The first report on the use of VGB as an add-on agent in the treatment childhood seizures documented that 6 out of 13 patients with IS had a favorable response (56). This was followed by a report from Chiron et al. (18) who studied 70 children with infantile spasms, all of whom had failed therapy with corticosteroids or other AEDs. Twenty-nine of these children (43%) responded with a complete cessation of their spasms. Especially remarkable was that 12 of 14 patients in that cohort whose underlying etiology of IS was tuberous sclerosis became seizure free. This is a particularly difficult subgroup to treat and previous studies have shown a very high relapse rate and overall poor response to treatment with ACTH (80). In a subsequent trial, Chiron et al. made a direct comparison between VGB and hydrocortisone (19) in infants with infantile spasms and tuberous sclerosis. In this study, 11 infants were randomized to VGB (150 mg/kg/d) and 11 to hydrocortisone (15 mg/kg/d). All 11 infants in the VGB group became seizure free, while only 5 out of 11 (45%) benefited from therapy with hydrocortisone. Seven out of the 11 on hydrocortisone (6 for lack of efficacy, 1 for adverse events) were crossed over to VGB and all of them became seizure free. This study lent substantial weight to the emerging argument that VGB should be considered as the first treatment of choice for IS due to tuberous sclerosis.

The Sabril™ (VGB) Infantile Spasms Investigator and Peer Review Groups in Europe retrospectively reviewed 250 patients who had received VGB and found that 192 had classical IS (2). The median dose was 99 mg/kg/d (range 30 to 200 mg/kg/d) and the seizures were controlled in 131 (68%) of the patients in about 4 d. Of the 131 who responded, 28 (21%) relapsed later. As demonstrated by Chiron and colleagues, patients with underlying tuberous sclerosis showed a dramatic response rate of 27 out of 28 (97%)
patients experiencing a cessation of spasms. Vigevano and Cilio (110) randomized 42 infants with IS to either VGB (100 to 150 mg/kg/day) or ACTH (10 IU/d) as first-line therapy; non-responders were crossed over to the other drug after 20 d. Cessation of spasms was observed in 11 (48%) of the patients randomized to VGB and in 14 (74%) of those randomized to ACTH. They concluded that VGB was more effective in patients whose etiology was cerebral malformations or tuberous sclerosis, and that ACTH proved more effective in those patients whose etiology of IS was attributable to perinatal hypoxia/ischemia. It is anticipated that, based on benefit to risk analysis, VGB will replace ACTH as the first choice of treatment for IS in the U. S. when it becomes available.

A large number of papers pertaining to the effect of VGB in children are retrospective reports and involve a wide range of ages and seizure types. We had summarized the results of several such studies (28,35,47,56,58,105,106,114) in a previous review (92). The initial report by Livingston and colleagues described best results with partial seizures and IS (56). Given the variations in the study designs and patient populations, the results are not easily compared. Nabbout et al. (70) have analyzed the result of therapy with VGB in 175 patients for partial seizures. In this population of patients ranging in age from 1 mo to 19 y ≥ 50% diminution in the frequency of seizures was seen in 70% of the patients, and 30% were found to be seizure free. A third of those patients who were seizure free could be maintained on VGB monotherapy. Belanger and associates reviewed the charts of 105 children who received either VGB or lamotrigine (LTG) as add-on therapy for intractable seizures and concluded that VGB was better in partial epilepsies and that LTG was superior in generalized epilepsies (5). They advance the notion that these two agents that are understood to work by different mechanisms be considered as components of rational polytherapy.

The analysis provided by Michelucci and Tassinari of the effect of VGB in adults with generalized seizures (64) and the animal data we have listed in the section on preclinical pharmacology would warrant caution in instituting therapy with VGB in children with generalized epilepsies. While one small series of patients with Lennox-Gastaut syndrome seem to have responded favorably to treatment with VGB (26), this is by no means a universal experience. It should also be cautioned that the patients who entered that study after failing to respond to VPA had not been tried on LTG, felbamate, or topiramate, all of which have demonstrated efficacy in this syndrome (1,24,37,67). Appleton (3) and Guerrini et al. (41) have cautioned about the possibility of VGB-induced worsening of childhood epileptic syndromes, especially myoclonic syndromes and absences.

**Behavioral Effects, Adverse Effects, and Tolerability**

When VGB was given to healthy human volunteers in a double-blinded, cross-over study, the differences between the drug and placebo were unremarkable. Compared to baseline, patients differed at the end of a 2-week treatment or placebo phase in only one out of the nine scales of cognitive function and mood (102). Depression, confusion, and other behavioral abnormalities account for about 5% of the reported AEs in epileptic patients treated with VGB. In 1991, Sander et al. reported psychotic reactions precipitated by VGB in 14 adult cases (85). Nine of these patients had no previous history of psychosis. With the exception of one patient who received an overdose of VGB, all the others
experienced resolution of their psychoses only upon discontinuation of VGB. Therefore, although some cases of psychosis may be dose- and/or titration-dependent, psychosis can also occur as an idiosyncratic reaction in susceptible individuals. The authors concluded that VGB should be started with caution in patients with severe epilepsy, particularly in the presence of a previous history of psychosis, and such patients should be carefully monitored. Sommerville et al. (97) concluded that patients with a mild psychiatric history were not at increased risk for exacerbation of their symptoms. Often, emergence of behavioral adverse events appears to be related to the rate of dosage titration. A retrospective survey by Thomas and colleagues suggested that psychosis as a treatment-emergent effect of VGB was associated with those patients who had very severe epilepsy and to a right-sided EEG focus, while depression as a treatment-emergent effect was associated with a past history of illness (103). Their study was not designed to estimate the incidence of these effects. Overall, the behavioral and psychiatric AEs noted with VGB were not out of proportion to those seen with other AEDs (113).

Hyperkinesia and agitation were reported in some children, most often in those treated with high doses of VGB (3). When the drug is discontinued or the dosage reduced all adverse effects (AEs) have been reversible. Chiaretti et al. (17) reported a case of acute psychosis in a child during treatment with VGB. In another case report, a 7-year-old boy with intractable epilepsy developed acute psychosis 3 d after initiation of a rapid VGB dosage escalation (16). All his symptoms resolved within 48 h after vigabatrin therapy was withdrawn. Two months later, reinitiation of therapy with VGB using a slower dosage escalation was well tolerated by the patient, and he continued treatment with VGB successfully.

VGB is very well tolerated compared with many other AEDs. Chronic treatment with VGB may be associated with a mild decrease in hemoglobin and with a decrease in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (47). Adverse effects reported in clinical trials are for VGB as add-on to other AEDs, up to four concomitant drugs. Sedation, fatigue, and dizziness appear to be the most commonly reported AEs. Some patients have also reported varying levels of difficulty with concentration, agitation, and emotional lability. Details of the AEs associated with VGB available from data on file with Hoechst Marion Roussel, as reported by Fisher and Kerrigan (27), reveal side effects resembling those seen with most AEDs, which are attributable to nonspecific CNS depressant effects.

TOXICOLOGY

Animal Studies

There has been significant concern with respect to the potential toxicity of VGB in humans as a result of the microvacuolization of white matter demonstrated in rodents and dogs. Microvacuolization was observed in the white matter of visual pathways, hypothalamus, columns of fornix, and cerebellar white matter (38). Doses as low as 30 mg/kg, well within the range used in humans, were found to cause intramyelinic vacuolization or edema in specific areas of rodent and dog brains (38). Sidhu and colleagues treated rat
pups with VGB from postnatal day 12 to 16 and assessed myelin at 19 to 20 d of age (94).
They observed decreased myelin staining in the external capsule, axonal degeneration in
white matter, evidence of glial cell death in the white matter, and reactive astrogliosis in
the frontal cortex. They did not detect myelin vacuolization. Ultrastructural examination
of the brains of beagles treated with VGB showed that the myelin sheath was split at the
interperiod line, producing the fluid-filled vacuole (13,14,115). This was not associated
with demyelination and only minimal axonal injury was evident. Time-dependent changes
were seen with increased severity with longer duration of exposure up to 12 mo. After
16 mo of oral treatment of monkeys at 300 mg/kg/d, any suggestion of intramyelinic ede-
ma was considered to be equivocal, and there was no evidence of any effect in the 50 or
100 mg/kg/d after 6 y of treatment (36). Higher doses caused chronic diarrhea, thus lim-
iting the dosage in this species. Monkeys treated with 160 mg/kg/d for 16 mo did not
have more microvacuoles at autopsy than the controls (36). In all animal studies, the
microvacuolization was not dose-dependent and was completely reversible with discon-
tinuation of the drug. Delayed conduction times using somatosensory and visual evoked
potentials (91) were found to correlate with the onset of vacuolization in dogs as detected
by MRI (111). Beagles treated with a 300 mg/kg dose of VGB developed MRI lesions
that were confirmed by histopathologic examination of the tissue (75,111) These lesions
developed progressively over 12 w, but seemed reversible upon discontinuation of the
drug.

Human Studies

No evidence of microvacuolization has been observed by magnetic resistance imaging
(MRI) in humans to date. Treatment for over 5 y with VGB doses ranging from 4200 to
9360 g/d in 11 patients did not result in discernible changes in the white matter signal by
MRI (20). No increased conduction times have been observed using evoked potentials in
long-term follow-up studies (10,46,55,100). Cannon and colleagues (15) reported 62 pa-
tients who had been treated with VGB and either had epilepsy surgery for intractable sei-
zures (52 patients) or had died (10 patients) and had detailed neuropathological exami-
nation of brain tissue. They did not find any of the neuropathologic changes seen in the
preclinical animal studies in these human cases. Observations by Hammond et al. (45) and
Sivenius et al. (95) are in agreement.

Another major concern for toxicity pertains to recent reports of severe persistent visual
field constriction associated with VGB (25,112). Eke and colleagues reported three such
cases (25) in which the symptomatic visual field constriction became apparent 2 to 3 y
after starting VGB treatment. The laboratory parameters in their cases suggest that the
outer retina rather than the optic nerve was damaged; however, the exact mechanism of
retinal damage is unknown. The effect did not appear to be reversible upon discontinu-
atution of the drug. Mackenzie and Klistorner (59) reported two asymptomatic cases of
visual field constriction in which perimetry revealed a binasal defect. Wilson and Brodie
(112) reported a similar case in which damaged retinal pigment epithelium and photore-
ceptors did not improve after discontinuation of VGB. The manufacturer of VGB has re-
ceived numerous reports (28 out of an estimated 140,000 patients as of January, 1997; Eke
1997) of such defects in patients treated with VGB (usually in combination with other
AEDs). The overall incidence, based on epidemiological studies is estimated to be 14.5/10,000 patients with epilepsy per year (60). Visual field constriction and blurring during VGB therapy seems to be associated with retinal cone system dysfunction (53).

While retinotoxic effects have not been commonly associated with AEDs, we did encounter a reversible case of toxicity to the pigmentary epithelium of the retina associated with CBZ therapy (71). A more recent study reported measurable retinal toxicity associated with PHT and CBZ, but not VPA (4). At the present time it is not clear what laboratory measure(s) could be used to monitor patients to help predict the likely emergence of symptomatic visual field defects; nor is it clear if early changes might be reversible upon discontinuation of treatment with VGB.

**CONCLUSIONS**

VGB appears to be a well-tolerated new anticonvulsant with demonstrated efficacy for partial and secondarily generalized seizures in adults and a distinctive pediatric utility profile. It appears to be devoid of hepatic or bone marrow toxicity. Dermatological reactions have not been reported in association with its use. Pharmacokinetic interactions are virtually absent. The lack of need for serum level monitoring, the superior tolerability, and its efficacy profile make VGB an important addition to the armamentarium of AEDs available to the clinician.

**REFERENCES**


