Epilepsia, **43**(8):812–817, 2002
Blackwell Publishing, Inc.

Clinical Research

The Effect on Vision of Associated Treatments in Patients Taking Vigabatrin: Carbamazepine Versus Valproate

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Summary: *Purpose:* To evaluate the effect on visual function of a concomitant antiepileptic drug (AED) in patients treated with vigabatrin (VGB).

Methods: Sixty-four consecutive patients with a history of partial seizures currently treated with VGB with either carbamazepine (CBZ) or valproate (VPA) were examined with automated kinetic perimetry, static perimetry, electrooculogram (EOG), and electroretinogram (ERG). An original device based on kinetic perimetry was developed to quantify the area of perception for each isopter.

Results: Fifty-two patients were finally included. The results showed a significant difference in patients treated with VGB-VPA compared with patients treated with VGB-CBZ concerning the mean defect of static perimetry and the peripheral and midperipheral isopter (III 4e and III 1a Goldmann equivalent, respectively) in kinetic perimetry. EOG and ERG results did not differ significantly between the two groups.

Conclusions: The visual impairment due to visual field constriction was more important in patients treated with VGB and VPA compared with patients treated with VGB and CBZ. The origin of this difference between the two associations could not be related to any particular retinal electrophysiologic abnormality. **Key Words:** Vigabatrin—Visual field constriction—Electrooculogram—Electroretinogram—γ-Aminobutyric acid.

γ-Aminobutyric acid (GABA) is an inhibiting neurotransmitter present in the brain and the retina. Vigabatrin (VGB) is an antiepileptic drug (AED) inhibiting GABA transaminase. Its pharmacologic action implies increased GABA levels in the brain and in the retina (1). Visual field abnormalities were first reported in a number of cases of VGB-treated patients in 1997 (2). Electroretinographic (ERG) recordings demonstrated abnormal cone responses (single flash and flicker) (3–5). In addition, oscillatory responses present on the ascending part of the ERG b wave in normal subjects could not be recorded in patients treated with VGB (6), which could implicate well-known highly GABAergic amacrine cells (7). Thus these findings were compatible with GABA-induced inner retinal dysfunction.

Electrophysiologic recordings of frog retinal pigment epithelium (RPE) also demonstrated that increased retinal (apical) GABA levels produce local ion-transport changes (8). In accordance with these in vitro studies on GABA turnover, functional changes of the outer retina within the photoreceptor–RPE complex were associated with VGB-attributed visual impairment in patients treated with this inhibitor of the GABA aminotransferase (9).

VGB is frequently prescribed in multi–drug-resistant epilepsia, in association with other AEDs. One of them, valproate (VPA), is likely to increase the inhibitory action of GABA in the retina (10). Previously the authors hypothesized that there might be an additive toxicity when VPA was associated with VGB in comparison with patients treated with carbamazepine (CBZ) and VGB (9). Patients taking VPA and VGB complained of peripheral scotoma and had more severe visual field constriction. However, the group of patients was too small to draw general conclusions, and static perimetry did not appear to be adapted to VGB-related peripheral visual field changes. For this reason, a method to quantify the results of kinetic perimetry was developed.

The purpose of this study was to compare the influence of the concomitant AED CBZ versus VPA on peri-

Accepted March 30, 2002.
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metric and electrophysiologic parameters in patients treated with VGB.

METHODS

Patients

All consecutive patients were diagnosed with partial seizures and had taken VGB and the associated drug, either VPA or CBZ for >6 months. Patients with high ametropia (>3 diopters), high astigmatism (>1.5 diopters), ocular hypertension (>21 mm Hg), or any additional underlying abnormality, such as glaucoma, tilted-disc syndrome, diabetes, oculomotor palsy, a history of strabismus surgery, or hemianopia that could interfere with perimetry or EOG were excluded from the study. Patients with a history of consecutive or concomitant treatment with both VPA and CBZ before inclusion were not included. Patients treated with any other AED than VGB, VPA, or CBZ were not included.

Procedures

A complete routine ophthalmologic examination was performed in all patients. Visual acuity was determined on an ETDRS chart. Slit-lamp anterior segment biomicroscopy, tonometry, and examination of the retina by indirect ophthalmoscopy was performed in all patients. Computer-assisted visual field examination was performed with a commercially available cupola stimulator (Vision Monitor, Pérenchies, France); the radius was 33 cm, and background luminance was 10 cd/m^2. A static 99-point 2-dB suprathreshold perimetry and a kinetic Goldmann-based perimetry was performed in these conditions. In the kinetic procedure, three isopters were tested at a speed of 2 degrees/s: the peripheral isopter (III 4e Goldmann equivalent) and two midperipheral isopters (III 1a and II 1c Goldmann equivalent). The eccentricities of initial stimulus presentation of each isopter were 90, 60, and 30 degrees, respectively. Blind-spot detection (III 4e Goldmann equivalent) was performed at 1 degree/s. No correction glass was used for the peripheral isopter; a correction in accordance with the refraction status was added for the two midperipheral isopters. The area of perception (in square degrees) was determined for each test without blind-spot subtraction. Three responses were averaged; each point was tested 3 times. If there was a difference of >10% between the best and the worst response, the procedure was repeated. A perimetric result was accepted only if the variability of each point was <10%. For each isopter, a moderate defect was defined by an area of <2 standard deviations (SDs) of the mean value obtained in normal subjects of the same age class. Three SDs was defined as severe defect. Figure 1 demonstrates a normal visual field.

Electrooculography (EOG) measured the variation of the standing potential of the eye between light- (500 candela/m^2) and dark-adapted conditions. In accordance with the standards of International Society for Clinical Electrophysiology of Vision (ISCEV), for each measure, six saccades were averaged to ensure accurate eye-movement performance (11).

Electroretinography (ERG) also was performed in accordance with ISCEV standards (12). The rod response, the maximal response, the oscillatory potentials, the cone response, and the flicker response were subsequently recorded. The amplitude and implicit time of each oscillatory potential was evaluated.

On recruitment, each patient provided informed consent to the procedures. The research followed the tenets of the Declaration of Helsinki.

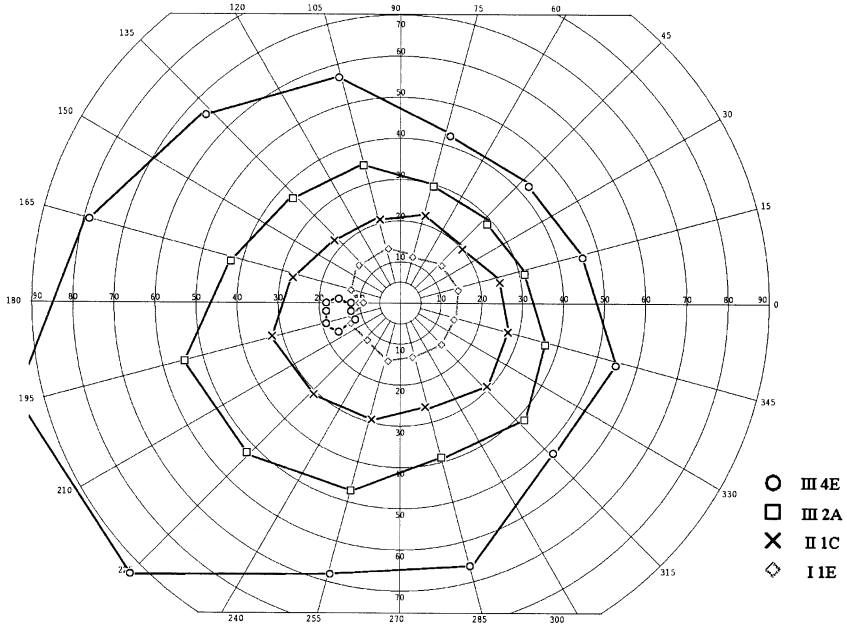

FIG. 1. A normal visual field of the right eye. In this study, only the III 4E, II 2A, and II 1C isopters were evaluated. The I 1E isopter shown was not analyzed in this study.

TABLE 1. *Comparing clinical parameters in patients treated with a combination of vigabatrin–carbamazepine (VGB–CBZ) and patients with vigabatrin–valproate (VGB–VPA)*

	Age (yr)	Seizure frequence (per mo)	Dose VGB (mg/kg)	Duration VGB (mo)	Cumulative VGB dose (g)	Dose CBZ/VPA (mg/kg)	Duration CBZ/VPA (mo)
VGB-CBZ	33.7	1.1 (0–2)	46.6 (35–72)	35 (10–96)	3,310 (360–10,800)	21.2 (CBZ) (14–30)	60.4 (12–288)
VGB-VPA	37.7	0.9 (0–2)	47.1 (31–70)	44 (12–120)	4,148 (270–11,520)	27.2 (VPA) (20–35)	58 (12–120)
Difference (p)	ns	ns	ns	ns	ns	ns	

Statistics

The different perimetric and electrophysiologic parameters were compared between the two groups by performing a Mann–Whitney *U* test. Spearman's correlation was used to evaluate the relation between duration, daily dose, and cumulative dose of VGB, with the visual parameters. A χ^2 test was performed to compare the rate of severe and moderate visual constriction between the two groups. Multivariant analysis was performed to determine whether age or VGB dose influenced visual field impairment in the two groups.

RESULTS

Global analysis

Initially, 64 consecutive patients were screened (Table 1). Twelve patients were excluded. One unreliable visual field testing in an 8-year-old child, one case of ocular hypertension, five patients with homonymous lateral hemianopia, three unreliable EOG recordings (one case of strabismus surgery, one case of retinal detachment surgery, and one case of laser treatment for diabetic retinopathy). Finally, two patients refused to undergo ERG.

The analysis was therefore conducted on a base of 52 patients, 26 male and 26 female patients, all having taken VGB for >6 months. All patients had a visual acuity of 20/25 or better, clear optic media, and no significant retinal or optic nerve head changes. The patients were separated into two groups depending on the associated AED, either CBZ (31 patients) or VPA (21 patients). No significant difference for age, seizure frequency, treatment duration with VGB, daily dose, or cumulative dose of VGB was found between the two groups (Table 1).

Visual field results

The visual field constriction, evaluated either by kinetic perimetry in terms of isopter area or by static perimetry in terms of mean defect, appeared to be significantly more important in the VPA group (Tables 2 and 3). This appeared to be especially important for the midperipheral isopter (III1A). Its area was nearly twice as large in the CBZ group (mean area: right eye, 3,267 square degrees; left eye, 3,032 square degrees) than in the VPA group (mean area: right eye, 1,502 square degrees; left eye, 1,757 square degrees). This difference between the two groups also was highly significant for the mean defect in static perimetry. The rate of severe and moderate visual field constriction was significantly higher in the group of patients treated with VPA (Table 3). Figures 2 and 3 represent two patients taking VGB, one with moderate visual field constriction (which was more commonly encountered in patients treated with CBZ) and one with severe visual field constriction, more common in patients treated with VPA.

Electrophysiologic results

The amplitudes of both the EOG and the ERG parameters were reduced in the VPA group. These differences did not reach statistical significance in any of the parameters analyzed (Tables 4 and 5). The implicit times did not either differ between the two groups (not shown).

Treatment with vigabatrin and visual function

A highly significant relation could be established in both eyes between duration of treatment and area of the peripheral III 4E isopter and also between the daily dose of VGB at the time of screening and the light/dark ratio

TABLE 2. *The visual field results of the two groups of patients*

		III 4E (°2)	III 1A (°2)	II 1C (°2)	Fixation loss	Attention loss	StatP (dB)	Fixation loss	Attention loss
RE	VGB-CBZ	8829	3267	1137	5.6%	6.8%	3.56	6.3%	5.5%
	VGB-VPA	5861	1502	783	5.3%	6.6%	7.0	6.6%	5.9%
	Difference (p)	<0.01	<0.001	ns	ns	ns	<0.001	ns	ns
LE	VGB-CBZ	8,650	3,032	1,040	5.4%	6.2%	3.87	5.6%	6.1%
	VGB-VPA	5,776	1,757	697	5.5%	5.9%	7.2	6.0%	5.8%
	Difference (p)	<0.01	<0.001	ns	ns	ns	<0.001	ns	ns

They appear to be significantly worse in the group of patients treated with the combination of VGB-VPA. RE, right eye; LE, left eye; StatP, suprathreshold 99-point static perimetry. The isopters in kinetic perimetry are given in square degrees (°2). The mean reliability parameters determined for each type of perimetry (kinetic and static) were comparable between the two groups.

TABLE 3. *Comparison of visual field results of patients treated with a combination of vigabatrin–carbamazepine (VGB-CBZ) and patients treated with vigabatrin–valproate (VGB-VPA)*

	RE III 4E	RE III 1A	RE II 1C	LE III 4E	LE III 1A	LE II 1C
Severe constriction (<3 SD)						
Vigabatrin–arbamazepine	8/31 (26%)	7/31 (23%)	2/31 (6%)	10/31 (32%)	6/31 (19%)	3/31 (10%)
Vigabatrin–valproate	14/21 (67%)	15/21 (71%)	5/21 (24%)	15/21 (71%)	14/21 (67%)	5/21 (24%)
χ^2, α	<0.05	<0.01	>0.05 (ns)	<0.05	<0.01	>0.05 (ns)
Moderate constriction (<2 SD)						
Vigabatrin–carbamazepine	13/31 (42%)	12/31 (39%)	8/31 (26%)	14/31 (45%)	18/31 (58%)	8/31 (26%)
Vigabatrin–valproate	17/21 (81%)	19/21 (90%)	14/21 (67%)	19/21 (90%)	19/21 (90%)	14/21 (67%)
χ^2, α	<0.05	<0.02	<0.05	<0.01	<0.01	<0.05

The group of patients with moderate visual field constriction includes all patients with *at least* moderate constriction and therefore also those with severe constriction.

of the EOG (both values of $p < 0.001$). No other significant correlations, in particular with the cumulative dose, were found.

DISCUSSION

In this series, patients treated with VPA and VGB have more severe visual field constriction, as assessed by both static and kinetic perimetry, compared with patients treated with VGB and CBZ. The exact origin of this possible combined toxicity remains to be explained. If a synergistic retinal action of VGB and VPA exists, then at least one of the electrophysiologic tests, assessing retinal function at different levels, should be clearly impaired in patients treated with this combination.

Concerning the pharmacologic action of VPA, a GABA-dependent action was previously suggested (13). In vitro, the association of VPA with GABA exerts a greater inhibitory action on the inner plexiform layer than does VPA alone (10). However, this level of action could not be confirmed in the present group of patients treated with VPA, as no significant difference was found between the two groups regarding amplitude or implicit time of the oscillatory potentials.

Besides reduced oscillatory potentials, visual field constriction due to VGB-related retinopathy has been associated with other electrophysiologic abnormalities, photopic ERG (3–6), scotopic ERG (5), and EOG changes (9).

As reduced amplitudes of ERG cone single-flash and flicker responses correlated significantly with severe visual field constriction, these parameters should preferentially detect retinal toxicity (4). The generation of the ERG b wave is believed to involve retinal glial cells (Müller cells) (14). If VGB inhibits GABA-transaminase activity known to be located in Müller cells, then this should greatly contribute to elevated GABA levels in the retina. The VGB-attributed reduction of ERG b-wave amplitude under scotopic and photopic stimulation con-

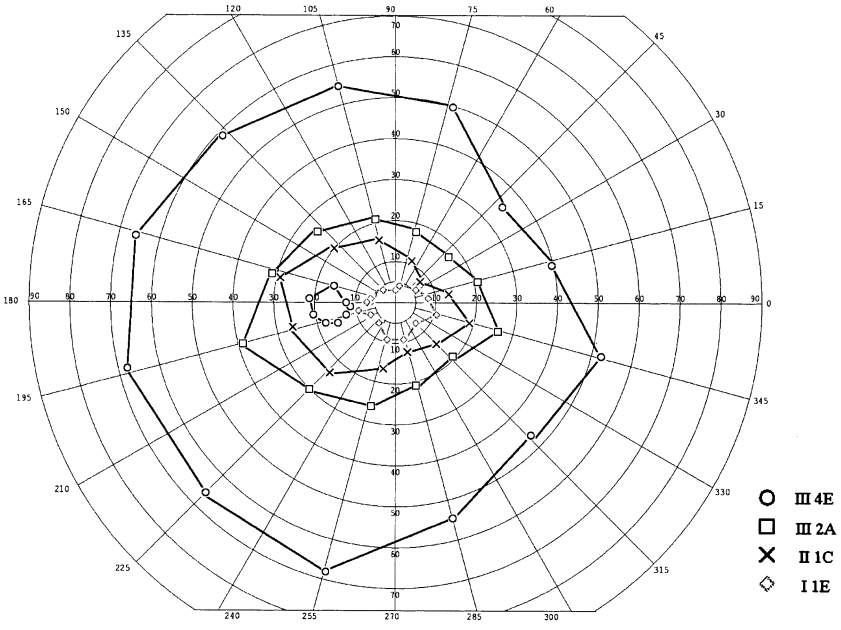

FIG. 2. The visual field of a patient with moderate constriction of the right eye.

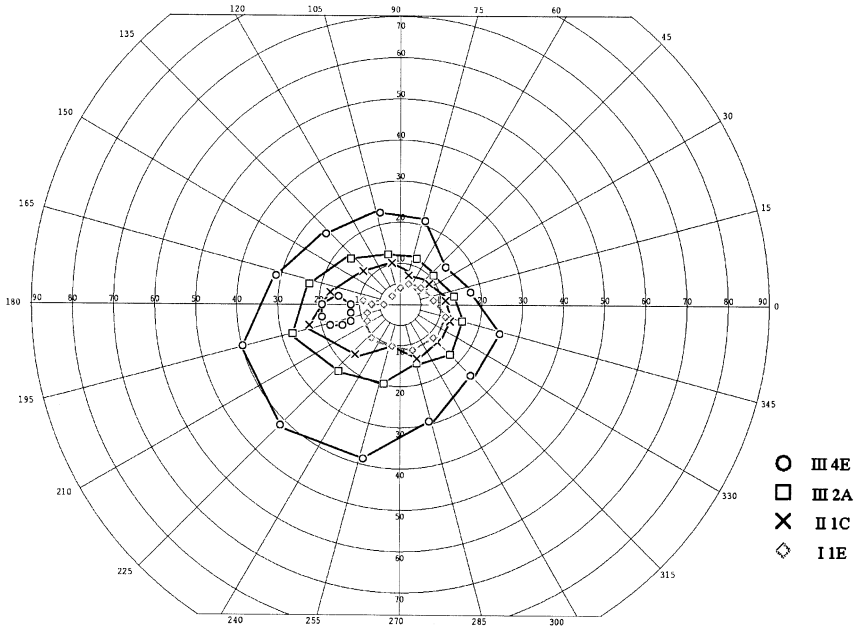

FIG. 3. The visual field of a patient with severe constriction of the right eye.

ditions could be the result of GABA-induced Müller cell dysfunction. No specific action of VPA on Müller cells has yet been reported. In the present study, although all ERG parameters were reduced in the VPA group in comparison with the CBZ group, neither the amplitude nor the implicit time of ERG single-flash and flicker responses was found to be significantly different in the VPA-VGB group compared with the CBZ-VGB group. This is concordant with current data concerning patients receiving VGB monotherapy, who demonstrated a similar frequency of abnormal findings in photopic ERG b wave, flicker b wave for both amplitude and implicit time, as did patients receiving VGB multitherapy (5). In the present study, it would have been interesting to include a group of patients receiving monotherapy with VGB, which, however, is an uncommon therapeutic scheme in Europe, as the use of VGB is restricted to multi–drug-resistant epilepsy. Therefore VGB is prescribed mostly in multitherapy regimens.

Unlike the ERG, the EOG is not considered a reliable indicator of visual impairment in terms of visual field constriction in patients treated with VGB (4,9). The strong correlation between the daily dose of VGB and the light/dark ratio suggests that the EOG reflects reversible VGB-induced metabolic changes, intraretinal GABA levels, which are known to be directly proportional to the daily dose of VGB in rats (15).

TABLE 4. *EOG results in patients treated either with vigabatrin–carbamazepine (VGB-CBZ) or vigabatrin–valproate (VGB-VPA)*

	Right eye			Left eye		
	Dark trough	Light peak	Light/ dark	Dark trough	Light peak	Light/ dark
VGB-CBZ	714.3	1,233.3	172.7	707.1	1,253.7	177.3
VGB-VPA	649.3	1,073.3	159.8	659.6	1,099.9	161.8
Statistics	NS	NS	NS	NS	NS	NS

The mean amplitude is considered for each group. No significant difference could be found between the two groups.

Although the mammalian RPE is not considered part of GABAergic neurochemical cycles, RPE cells also possess a dual taurine/GABA transporter (16,17). However, no major GABA turnover rate can be expected in the RPE (18), as no significant GABA concentrations normally develop in the subretinal space. The RPE uptake of taurine is known to be completely inhibited by an excess of subretinal GABA (19), suggesting that the common transport process, the taurine/GABA transporter, operates in the uptake of these two compounds. In patients treated with VGB, this could result in an excess of taurine, which is known to depress the b-wave signal in the frog retina (20). Inhibited taurine transport might thus explain the observed cone dysfunction in patients treated with VGB (6).

In addition, VPA is known to increase taurine levels in the brain (21,22). The effect of VPA on the retinal pigment epithelium is not known; however, VPA modifies ion transport across the epithelium of the choroid plexus (23–26), which presents major similarities to the retinal pigment epithelium concerning especially the apical situation of the Na/K pump. The EOG reflects outer retinal function including ionic currents across the RPE. If there were a synergistic effect of VGB and VPA on visual field constriction, then the light/dark ratio of the EOG should be reduced in patients treated with this combination compared with patients taking VGB-CBZ. In the current

TABLE 5. *ERG results in patients treated either with vigabatrin–carbamazepine (VGB-CBZ) or vigabatrin–valproate (VGB-VPA)*

	Rod a RE	Rod b RE	Rod a LE	Rod b LE	Max a RE	Max b RE	Max a LE	Max b LE	Cone a RE	Cone b RE	Cone a LE	Cone b LE	Flicker RE	Flicker LE
VGB-CBZ	−14.2	168.2	−13.6	165.5	−243.0	416	−203.8	424.4	−44.6	104.7	−46.2	103.0	75.1	74.7
VGB-VPA	−9.2	151.0	−12.6	159.6	−256.3	379.3	−270.8	385.6	−41.7	90.8	−42.8	91.1	60.7	62.2

The mean amplitude is considered (a and b wave of the rod, max and cone response, peak-to-trough amplitude of the flicker response). No significant difference could be found between the two groups.

ERG, electroretinogram.

study, all parameters of the EOG were reduced in the VPA-VGB group compared with the CBZ-VGB group, although none reached statistical significance.

In this group of consecutive patients, the visual field appears to be clearly more altered in patients treated with VPA. Although no particular level of VPA-related additive retinal toxicity could be identified by the electrophysiologic tests, this should be kept in mind when the combination of VGB and VPA is prescribed.

Acknowledgment: We thank Dr. Jean-Marie Jaquesson for his advice in statistics. This sutdy was supported by grants from Programme Hospitalier de Recherche Clinique 98-1957 du Centre Hospitalier et Universitaire de Lille provided by the Direction de l'Hospitalisation et l'Organisation des Soins, France, and a research grant from Aventis Pharmaceuticals, Inc., in 1999.

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