SYNOPSIS

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Study number : 4102

Study title : Follow-Up Screening to Investigate the Occurrence of Long-Term Retinal Effects in Children Exposed to Vigabatrin Treatment and in Subjects Exposed to Vigabatrin In Utero

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PDF name: Vigabatrin-Study 3

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Follow-Up Screening to Investigate the Occurrence of Long-Term Retinal Effects in Children Exposed to Vigabatrin Treatment and in Subjects Exposed to Vigabatrin In Utero
(Study #4102)

Study Report
September, 2000

Background

Several studies and pooled analyses have estimated the prevalence of vigabatrin-attributable visual field defects (VGB-VFD) to be 20% to 40% in the adult population, depending on the study, country, and cumulative exposure to the drug. There have been no formal studies of the prevalence of VGB-VFD in children. To examine the occurrence of this defect in young children, an observational study was designed to quantify the prevalence of VGB-VFD in this population of patients.

Study Design

This was a Phase IV Cross-Sectional Study designed to quantify the prevalence of persistent visual field defects in children after exposure to vigabatrin and among subjects exposed to vigabatrin in utero. In addition, the diagnostic performance of the H-Stimulus Test (which was designed to detect visual field defects in children) and ERG were evaluated in comparison to standard perimetry.

Patients with infantile spasms or refractory partial epilepsy exposed to vigabatrin for at least three months, and subjects exposed to at least one dose of vigabatrin in utero were recruited. Patients with potential for non-compliance or a confirmed diagnosis of bilateral optic atrophy or registered blind were excluded from the study. Patients were not taking any study medications apart from their usual treatment for epilepsy as determined by their physician. Three centers in the U.K. were included in the study to recruit potential study subjects. The projected sample size at the time of inception of the study was approximately 95 patients: 35 with infantile spasms, 50 with refractory partial epilepsy, and 10 subjects exposed to vigabatrin in utero. After consultation with the centers, though, it was evident that this sample size would not be achievable and that every effort would be made to recruit as many patients as possible.

Demographic information, relevant medical/surgical history, epilepsy history, use of antiepileptic medications or other concomitant medications, use of steroids, ophthalmologic history, and the occurrence of adverse events (as a result of study procedures) were collected at the first visit. In addition, ERG, H-Stimulus, and standard perimetry (if developmental age ≥9) tests were performed at this time. If appropriate, additional visits were scheduled for follow-up testing (perimetry) if this procedure could not be completed or was not reliable at the time of the first visit. Results of the ERG, H-Stimulus Test and perimetry were sent to experts for subjective evaluation of the presence of VGB-VFD.
Statistical Analysis

Univariate statistics were compiled to examine the distribution of age, gender, eye color, duration and average daily dose of vigabatrin therapy. To determine the prevalence of VGB-VFD in this population, a positive perimetry test was used as the “gold standard”. The diagnostic performance of the H-Stimulus Test and ERG was assessed using standard 2 X 2 tables for the calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. Logistic regression models were fit to assess the ability of specific ERG and H-Stimulus parameters to predict a positive perimetry result (true case). In addition, cutoff points in specific parameters of the ERG test (30 Hz flicker a-b amplitude) and H-Stimulus Test (N135 and P100 amplitude) were examined to mimic or increase the precision of the experts subjective responses.

Results

Forty subjects were recruited into the study. One patient who completed the study was in violation of the study protocol. This patient (patient #003/010) was not exposed to vigabatrin for three months, thereby leaving a total sample size of 39 patients. Twenty-six patients completed ERG testing (at least 1 of the ERG tests), 35 patients completed the H-Stimulus Test, and 12 patients had reliable perimetry results. In this population of children, compliance was highest with the H-Stimulus Test followed by ERG. Less than one-third of patients could perform perimetry.

Of the 39 patients who completed the study, 92.3% were treated for refractory partial epilepsy and 7.7% for infantile spasms. There were no subjects in the study exposed to vigabatrin in utero. The mean age of the patient population was 9.4 years (median=10 years, SD = 3.5 years, range =3-15 years) and the majority of the patients were male (69.2%). Almost 44% of patients had blue eyes, 23% had brown eyes, 13% hazel eyes, 10% gray eyes, 8% green eyes, and 3% unknown color. The mean duration of vigabatrin use was 2.20 years (SD=1.89 years, range=0.18-8.34 years) and the mean daily dose of vigabatrin was 1,399.43 mg (SD=801.17 mg, range 402.64-3,949.81 mg).

Twelve patients (30.8%) had reliable visual field examinations. The remaining 27 patients could not perform perimetry. Of these 12 patients, six were evaluated with the Humphrey Field Analyzer (HFA) Program 30-2, five patients were evaluated by the 135 program, and one patient was evaluated by both the 135 program and Goldman perimetry. According to the study protocol, visual field testing was to be done with the HFA Program 120, followed by the HFA Program 30-2 if a defect was suspected. Since none of the patients were tested with the HFA Program 120, a positive result on either the 135 or the 30-2 program was considered positive for a VGB-VFD. If the result of any visual field test was considered as the “gold standard”, the prevalence of VGB-VFD was 33.3% (4/12). The small sample size prohibited stratification of the prevalence by indication for vigabatrin treatment as well as any examination of the role of age, gender, eye color, duration or dose of vigabatrin therapy as possible predictors of VGB-VFD.

If the result of any reliable visual field examination was considered the “gold standard” in the assessment of the diagnostic performance of the H-Stimulus Test, the sensitivity of the test as subjectively determined by the expert was 75%, the specificity was 75%, the PPV was 60%, and the NPV was 85.7%, therefore resulting in a diagnostic accuracy of 77.8%. The comparable
values for the diagnostic performance of ERG were 25%, 75%, 33.3%, and 66.7%, respectively, with a diagnostic accuracy of 58.3%. Since it would be advantageous to try and quantify the prevalence of VGB-VFD in the total population of 35 patients with H-Stimulus Test results, we used the distribution of false-positive and false-negative results from the diagnostic performance evaluation to estimate prevalence of VGB-VFD. Assuming the marginal distribution of the H-Stimulus Test results was fixed, we then allocated the results of the H-Stimulus Test for the 35 patients in the same proportions as found for the 12 patients who had reliable visual fields. Using this approach, the resulting prevalence of VGB-VFD in these 35 patients was 25.7%.

For the patients who had reliable visual field examinations, we also looked at individual parameters of the H-Stimulus Test (P100 amplitude and N135 amplitude, both evaluated for the left and right visual cortex) and ERG (30 Hz flicker a-b amplitude) to determine whether or not there was a correlation between any of these parameters and the perimetry results. Logistic regression analyses did not reveal any statistically significant parameters that were predictive of VGB-VFD.

We also looked at cutoff values for the P100 and N135 (left and right visual cortex) parameters to determine if there was a value or algorithm that would provide equivalent or improved sensitivity and specificity compared to the expert’s subjective assessment of VGB-VFD. There was no value or algorithm for the P100 amplitude that mimicked the sensitivity or specificity of the expert’s subjective assessment of VGB-VGD. An algorithm for the N135 amplitude was identified that provided better diagnostic performance than the expert’s subjective assessment of VGB-VFD. This algorithm, defined as the sum of the N135 amplitude left visual cortex and the N135 amplitude right visual cortex, where if both the left and right eye had values of less than 10 micro volts, resulted in a sensitivity of 75%, specificity of 87.5%, PPV of 75%, and NPV of 87.5%. The overall diagnostic accuracy using this algorithm was 83.3%. These diagnostic performance values were based on the 12 patients with reliable visual field tests. In addition, we were able to improve the diagnostic performance of ERG relative to the expert’s subjective assessment using the 30 Hz a-b amplitude values. Using a cutoff value of less than 70 micro volts in both eyes for the 30 Hz a-b amplitude results in a sensitivity of 75%, specificity of 75%, PPV of 60%, NPV of 85.7%, and diagnostic accuracy of 75%.

Conclusions

Only 12 patients in this study population had reliable visual field examinations from which to estimate the prevalence of VGB-VFD and evaluate the diagnostic performance of the H-Stimulus and ERG tests. Based on this small sample of patients, the prevalence estimates of 33.3% (based on 12 patients) and 25.7% (based on 35 patients) does not provide evidence that the proportion of children exposed to vigabatrin and testing positive for VGB-VFD differs from that of the adult population.

The H-Stimulus Test had a sensitivity of 75% and specificity of 75% based on subjective expert opinion compared to standard perimetry. Only four patients were found to have a VGB-VFD according to perimetry. One of these patients (#001/006) was both subjectively and objectively defined as “normal” according to both the H-Stimulus and ERG results. Objective evaluation of the H-Stimulus Test using the N135 amplitude (left and right visual cortex) increased the specificity of the test from 75% to 87.5%.

The diagnostic performance of ERG was poor based on subjective expert assessment. Further analysis, though, revealed that the 30 Hz a-b amplitude objectively provided an adequate
sensitivity and specificity when a cutoff value of less than 70 micro volts was used. This increased the sensitivity from 25% to 75% and kept the specificity constant at 75%.

It is clear that the H-Stimulus Test can be satisfactorily performed by 90% of children with epilepsy with a chronological age of three or older. This test has a diagnostic accuracy of 83.3%. Sixty-seven percent of children can comply with the ERG protocol using DTL electrodes with no sedation. This test results in a diagnostic accuracy of 75%. The H-Stimulus Test appears to be more acceptable to young children than ERG in this study population.

To test the validity and reliability of the algorithms used to evaluate the diagnostic performance of the H-Stimulus and ERG tests in young children, additional patients should be evaluated with these methods and the algorithms applied. Acceptance of these algorithms as a replacement for subjective evaluation of test results without further assessment would be premature. Should further testing reveal that the methods used in this study are applicable to similar children with epilepsy, objective evaluation of these tests may preclude the need for subjective opinion in future testing.