The Royal College of Ophthalmologists

The Ocular Side-Effects of Vigabatrin (Sabril)

Information and Guidance for Screening

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Background

Vigabatrin (Sabril) is an anti-epileptic drug indicated for the treatment of partial epilepsy, with or without secondary generalisation, which is not satisfactorily controlled by other drugs. It is only licensed as first-line/monotherapy for the treatment of infantile spasms (West's syndrome). While vigabatrin was being clinically developed, only rare cases (<1:1000) of symptomatic visual field constriction and retinal disorders were reported. Visual field defects in patients taking vigabatrin have been reported since the drug was first marketed in the UK in 1989. In 1997, 3 cases of severe, symptomatic, persistent visual field constriction associated with vigabatrin treatment were described.[1] In 1999 the Committee on Safety of Medicines (CSM) and the Medicines Control Agency (MCA) responded by advising that vigabatrin therapy should only be initiated by an epilepsy specialist and in clinical situations where all other anti-epileptic therapies had not been effective or tolerated. Further, the drug should be prescribed to a maximum dose of 3 g daily in adults, and should be gradually withdrawn if no clinical benefit is obtained. In addition, vigabatrin is not recommended for patients with pre-existing visual field defects. A NICE Technology Appraisal in 2004 found that there was no convincing evidence for superiority of seizure control by vigabatrin compared with alternative therapies in either partial seizures or West's syndrome. However, the risk of visual field constriction attributable to vigabatrin (VAVFC) must be balanced against the adverse effects of alternative therapies, and of uncontrolled epilepsy, and vigabatrin therapy remains an important option in this group. Overall, it appears that the use of vigabatrin as an antiepileptic drug is declining.[2]

Pharmacology

Vigabatrin acts as a selective irreversible inhibitor of GABA-transaminase. Treatment therefore causes an increase in the concentration of GABA (gamma aminobutyric acid), the major inhibitory neurotransmitter in the brain. The duration of effect is dependent on the GABA transaminase re-synthesis rate. The drug is water-soluble, and is rapidly absorbed from the gastrointestinal tract. It is eliminated unchanged renally; it is neither metabolised nor protein bound so drug interactions are unlikely. Maximal efficacy in adults is usually seen in the 2-3 g/day range. The recommended maintenance dose in children is 50-100 mg/kg/day.

Clinical Features

Symptoms

Patients with perimetric loss due to vigabatrin exhibit normal visual acuity, and are usually asymptomatic of the field loss unless the defect encroaches within the central field.[3] This appears to be the main explanation for the vast underestimation of VAVFC prevalence in early studies, which relied on self-reporting of symptoms. Symptomatic patients have complained of blurred vision, oscillopsia, tunnel vision, and difficulty in navigation. They do not always recognise that these problems are due to visual reduction, and may attribute them to clumsiness or drowsiness.[4]

Fundus features

Visual field loss can exist in the absence of any demonstrable fundal pathology observed clinically. However, optic nerve head pallor and retinal nerve fibre layer (RNFL) atrophy have been demonstrated in subjects taking vigabatrin. RNFL and optic atrophy show a significant correlation with VAVFC and cumulative vigabatrin dose.[5] In one study, patients with VAVFC displayed a reduced mean RNFL thickness compared with those taking vigabatrin without field loss.[6] This study found that optical coherence tomography (Stratus OCT, Carl Zeiss Meditec) showed promising sensitivity in detecting RNFL atrophy associated with vigabatrin field loss. Larger trials are required to confirm the potential usefulness of imaging techniques, especially in patients unable to perform perimetry. Other subtle fundoscopic features associated with vigabatrin use include surface retinal wrinkling, peripheral retinal arteriolar narrowing, and irregular sheen or abnormal pigmentation at the macula.[7]

Visual function and perimetric methods

Vigabatrin is associated with bilateral, concentric, predominantly nasal constriction of the visual field. The prevalence of VAVFC varies widely between studies, but is generally estimated to be 30-40%.[8-10] The Marketing Authorisation Holders survey (involving 335 patients over 14 years old taking vigabatrin) found that 31% of subjects had VAVFC (95% confidence interval 26-36%). VAVFC shows a characteristic pattern of concentric peripheral field loss with temporal and macular sparing. Mild cases may exhibit binasal field loss. The defect is usually absolute, and typically does not affect the central field. However, there have been reports of reduced central visual function, including reduced sensitivity,[11] reduced contrast sensitivity,[12] and acquired colour vision defects.[13] In a minority of patients VAVFC has been so severe that it limited their ability to perform a variety of activities of daily living. Vigabatrin can also be a cause of not achieving a satisfactory driving visual field.[14] Given the spectrum of disorders of visual function associated with vigabatrin, it is recommended that vigabatrin should not be given with other retinotoxic agents.

Whilst the majority of defects extend to within 30 degrees of fixation, defects outside that eccentricity, and therefore not detected by standard 30 degree threshold tests, have been reported. This finding is in accord with a study that

found that peripheral rod-derived dark-adapted visual fields were also constricted in patients having VAVFC on light-adapted fields.[15] Another study demonstrated that VAVFC was detected more frequently using automated static perimetry than with manual kinetic perimetry.[10] In addition, the prevalence of VAVFC is generally found to be higher in studies using automated static perimetry compared with those using manual kinetic perimetry.[10, 16] This suggests that VAVFC is more sensitively detected by the former technique. Whilst a developmental age of at least 9 years is usually required to produce reliable perimetry, visual fields can be assessed in younger subjects. Specifically developed techniques such as arc perimetry based on forced-choice, preferential-looking methods have shown promise in detecting VAVFC in subjects younger than 9 years.[17]

Electrophysiology

1. Visual Evoked Potential (VEP)

Most studies on subjects with VAVFC have demonstrated standard VEP responses to be within normal limits. In an industry-funded study, Harding *et al* developed a field-specific VEP eliciting responses from the central 0-5 degree and peripheral 30-60 degree fields.[18] Responses were obtained in cooperative children as young as 3 years. In 39 children treated with vigabatrin for partial epilepsy, 35 were able to produce reliable field-specific VEP tests. When compared with the 12 children who were able to produce reliable perimetry, the test gave a sensitivity of 75% and specificity of 87.5%. Sanofi-Aventis make the algorithm available free of charge to test for VAVFC in children over 3 years. However, the diagnostic accuracy of field-specific VEP testing needs to be validated in larger studies and cannot at this stage be recommended as a means of detecting VAVFC.

2. Electroretinogram (ERG)

VAVFC is associated with ERG abnormalities such as increased photopic b-wave latencies, reduced b-wave amplitude, and reduced or absent oscillatory potentials.[4] Correlations between the severity of the ERG changes and duration of therapy as well as severity of VAVFC have been shown. Some of the ERG changes occur in the absence of VAVFC, due physiologically to raised retinal GABA levels. However, one study found the amplitude of the cone flicker response to be the strongest of all the ERG parameters in predicting VAVFC with a sensitivity of 100% and a specificity of 75% in 26 patients exposed to vigabatrin and 22 normal subjects.[19]

3. Electro-Oculogram (EOG)

A reduced Arden Index is frequently found in patients with VAVFC,[4] although it has been noted in patients taking vigabatrin but without visual field loss.[20] In addition, it has been observed that a reduced Arden Index measured whilst a patient is taking vigabatrin returns towards normal when the drug is stopped, whilst VAVFC persists.[8] This has led to the suggestion that the reduced Arden Index reflects drug efficacy rather than toxicity.

Risk Factors

Patient sex

Males on vigabatrin have an increased risk of developing VAVFC of approximately 2-fold compared with females.[4, 10] This effect appears to be

independent of any differences in dose duration or cumulative dose of vigabatrin.[21]

Treatment dose and duration

Several studies have not identified a relationship between the daily or cumulative dose of vigabatrin and the risk of VAVFC. It has therefore been postulated that the drug response is idiosyncratic in nature. By contrast other studies, with more precise data on dose and duration of vigabatrin, have found clear correlations between cumulative drug dose and duration and prevalence of VAVFC. Malmgren *et al* found VAVFC in 2/51 patients (4%) with cumulative doses less than 1 Kg, but in 10/14 patients (71%) with cumulative doses greater than 3 Kg.[22] A review which explored the relationship in different studies between cumulative dose (where data available) and VAVFC prevalence found a cumulative risk plateau at 5 Kg.[16] Cumulative doses above this level did not appear to impart any further increase in risk. VAVFC below a cumulative dose of 1 Kg was uncommon, with prevalence rising steeply at cumulative doses between 1 and 3 Kg. Cumulative dose of vigabatrin has also been correlated with severity of VAVFC.[21, 23] Hardus *et al* analysed the relationship between a carefully documented cumulative dose of vigabatrin and percentage loss of the visual field as measured using the Goldmann V/4 stimulus.[21] Linear regression analysis revealed a clear correlation between cumulative dose and percentage field loss (r=0.49; p<0.001), although data points were widely scattered. Multiple linear regression selected cumulative dose as the parameter explaining significantly the relationship with percentage field loss; dose duration did not contribute further to the precision of the model. Whilst it seems clear, then, that cumulative dose is related to VAVFC prevalence, the position on duration of treatment is less clear. Healthy volunteers exposed to a short duration of vigabatrin demonstrated no detectable effect on visual field.[20] Whilst reports are present of VAVFC developing after just a few months of treatment, the vast majority of reported cases occur after 1 year. The Marketing Authorisation Holders Survey (335 patients on VGB aged over 14 years) found that the cumulative incidence of VAVFC rises rapidly in the first 2 years and first 2 Kg of intake, then stabilises after 3 years/ 3 Kg. One study comparing the prevalence of VAVFC in patients taking vigabatrin for less than, or more than, 4 years found rates of 31% and 28% respectively.[24]

Patient age

Visual field assessment is much more difficult in children than in adults and estimates of VAVFC are accordingly scarcer. Such estimates have varied significantly between studies. A review by Lawden calculated the overall prevalence of VAVFC amongst the studies of paediatric patients to be 29%, slightly lower than the adult figure.[16] However, most paediatric studies used kinetic perimetry which may be less sensitive at detecting VAVFC. In addition, paediatric patients tend to produce more variable visual field results making the distinction between normality and disease more difficult.[25] There is no information on the possible occurrence of VAVFC in children who have been exposed to vigabatrin in utero. Currently it is recommended that vigabatrin should only be used during pregnancy if clearly necessary. Vigabatrin is

excreted into breast milk and breast feeding during treatment with the drug is not recommended.

Prognosis

The vast majority of studies indicate that VAVFC does not reverse on cessation of the drug, although reports of reversibility are present in the literature.[26, 27] However, great caution must be applied in concluding that VAVFC can resolve on stopping the drug, since a common cause of visual field loss is artefact, with the apparent defect improving over subsequent tests due to the visual field learning effect.[28] Whilst VAVFC can worsen if vigabatrin is continued,[29] one study found that established VAVFC in patients who had taken treatment for at least 5 years, and who elected to continue, did not tend to worsen over a period of at least 18 months follow up.[30] Whilst it seems sensible to recommend that screening be undertaken, where possible, to detect asymptomatic VAVFC, there is no good evidence available that intervention at the pre-symptomatic stage improves outcome. However, knowledge of visual field function will allow a more informed consent process.

Recommendations

A. Screening for VAVFC in subjects able to perform perimetry

Visual field testing is generally feasible in subjects with a developmental age of at least 9 years. Such patients taking vigabatrin should undergo a visual field examination to exclude the possibility of visual field loss. This may comprise a static suprathreshold two zone or three zone age corrected strategy to at least 45 degrees of eccentricity (for example Humphrey 120 point or Octopus 07), or Goldmann kinetic perimetry (III - 4e and I - 4e or I - 2e stimuli, as appropriate), although kinetic perimetry is likely to be less sensitive. If VAVFC is detected it is advisable, if possible, to conduct a confirmatory field test within 1 month before considering cessation of vigabatrin. A threshold test extending to 30 degrees of eccentricity (for example Humphrey 30-2) may be used and might allow extra precision, particularly in detecting progression. If the drug is discontinued perimetry should be repeated at a future date to monitor the field loss. Threshold testing is not generally recommended as a screening strategy because of the increased testing times, and therefore fatigue, associated with testing to at least 45 degrees of eccentricity.

Timing

A baseline visual field should be obtained before starting treatment. Perimetry should then be repeated every 6 months for five years. It can then be extended to annually in patients who have no defect detected.

B. Screening for VAVFC in subjects not able to perform perimetry

Patients with a developmental age less than 9 years are not typically able to produce reliable visual field testing. In addition, approximately 20% of adults with epilepsy are unable to perform reliable automated perimetry.[19] Such patients represent a particular difficulty because, at present, no validated

method is available for detection of VAVFC. Further studies are urgently required to confirm the diagnostic accuracy of field-specific VEP. Where this technique is used and an absent peripheral response is found with a normal central response the risk-benefit balance of vigabatrin continuation should be discussed further with the patient and carers. ERG techniques are unlikely to be of wide benefit due to the practicalities of and compliance with these methods in children.

C. Discussion with patients and carers

It is the responsibility of the prescribing doctor to discuss with the patient, or the patient's relatives or carers, the risks of VAVFC. As the degree of field loss may be severe enough to limit driving and even daily activities, the potential risk needs to be assessed against the potential benefit of seizure control. Patients should be alerted to report any abnormalities in their vision, and must be informed of any abnormalities in visual field tests. They should be advised that VAVFC can worsen if the drug is continued, although it may remain static, particularly if the duration of treatment is greater than 5 years or the cumulative dose is greater than 5 Kg. Progression of VAVFC after stopping vigabatrin has not been reported to date.

Conclusions

There are still many unanswered questions concerning the relation between vigabatrin and visual field defects. Evaluation of the clinical situation is difficult when it comes to assessing the potential risk to the patient, particularly where children are concerned. It is a matter for the prescribing paediatrician or neurologist to weigh up the dangers of potential side-effects against seizure control and to instigate screening for VAVFC. Despite the additional workload that visual field screening for patients on vigabatrin adds to already overburdened eye departments, accurate visual field monitoring will enable a more informed decision on whether to initiate or continue treatment with vigabatrin.

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March 2008

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