Editorial

Vigabatrin: An Antiepileptic Drug with Major Benefits but Significant Adverse Effects

As is the case for most drugs, vigabatrin (VGB) has major advantages and also has significant adverse effects. However, the situation for VGB is somewhat unusual. The drug was prescribed for many years before Eke *et al*. [1] reported peripheral visual field defects (VFDs) in three adult patients. Other adverse effects [2], including psychiatric changes and transient MRI abnormalities have been reported but will not be discussed here. VFDs appear to be common, having been found in 25% to 50% of adult patients taking VGB [2]. Although the VFDs are asymptomatic in most patients [3, 4], this must be viewed as a serious adverse effect. For example, those with horizontal visual fields less than 120˚ are not permitted to hold a driving licence. Visual acuity is not usually affected and, although those with VFDs retain an average lateral visual field of 65˚ [5] (i.e., 130˚ horizontal), sometimes the visual field constriction may be severe [3]. There is debate about whether the VFDs are reversible [6, 7] but a number of reports have suggested that they are not [8, 9]. Does the emergence of this frequent, serious, and possibly irreversible adverse effect imply that VGB should no longer be prescribed or should be withdrawn from the market? The recent FDA approval would suggest that this is certainly not the case. What is the justification for the availability of this drug? VGB is almost unique in having an apparently single, intended mode of action, namely inhibition of GABA-transaminase, the enzyme that breaks down the inhibitory neurotransmitter GABA, with result that GABA concentrations in the brain are increased. It can be of benefit in treating partial-onset seizures in some patients for whom no other drug has been effective. VGB also has a major role to play in the treatment of infantile spasms, a very severe form of epilepsy with a high risk of poor outcome, both in terms of ongoing seizures and in terms of significant cognitive impairment [10]. If the infantile spasms are secondary to tuberous sclerosis, VGB appears to be particularly effective; in the initial studies 100% of the babies became spasm free [11]. In subsequent studies the response rate has been less but has remained very high. The other effective treatment for infantile spasms is ACTH or steroids, which can be also associated with serious adverse effects [10].

How is the clinician to weigh the risk of the serious adverse effect of VFDs against the possible advantage of good seizure control? In the case of partial-onset seizures, the decision-making process might be easier because the advantages and disadvantages can usually be discussed directly with the patient, who can then make an informed decision. However, this is not always the case. One of my patients was a wheelchair-bound teenager with severe learning disability (mental retardation) and severe epilepsy, in whom good seizure control had been achieved with VGB. Another clinician stopped the VGB because of concerns about the possibility of VFDs. If this patient had developed visual field constriction, it would almost certainly not affected his quality of life, which was much more severely impaired by his other problems and which was certainly very severely decreased when the uncontrolled seizures returned. After consultation with his carers, the VGB was re-instituted, with a good response.

The remainder of the discussion will concentrate on infantile spasms because the situation with this severe form of epilepsy is very different. Because the onset is typically around 4 to 9 months of age, it is up to the parents or carers to decide on treatment, in discussion with the clinician. Concerns about possible VFDs may weigh heavily with parents. They might also have difficulty in appreciating what the implications of this possible adverse effect could be for their child. What guidance can be given? To answer this question, further information is required. Perhaps the best way of considering this situation is to ask a series of additional questions. Several of these issues are discussed in the excellent review by Willmore *et al.* [2].

Have visual field defects been described in children who took VGB for infantile spasms as infants?

What is the minimum period or minimum dose of VGB that has resulted in apparently permanent visual field defects?

If the VGB is stopped at the first sign of VFDs, will this adverse effect be less than it would have been if the VGB had been continued?

Is there any evidence that treating infantile spasms promptly and effectively changes prognosis, particularly with regard to cognitive outcome?

Which is superior in treating infantile spasms, VGB or ACTH/steroids; should different treatments be favoured in different circumstances?

If the infantile spasms stop with VGB treatment, how long should this treatment be continued; should this decision be influenced by the risk of visual field defects?

These questions will be addressed in turn.

First, what is the evidence for VFD in children in who took VGB in infancy? Gaily *et al*., [12] examined visual fields by Goldman kinetic perimetry in 16 children aged 6-12 years who had taken VGB in the first two years of life. The VGB was started at a mean age of 7.6 months (range 3.2-20.3) and continued for a mean of 21.0 months (range 9.3-29.8). The mean cumulative dose was 655g (range 209-1109). Mild VFDs were detected in only one of the 16 children; this child had been treated for 19 months and had received a cumulative dose of 572g. The authors concluded that the risk of VFDs might be lower in this age group than in older children or adults. However, the number of subjects was small, implying broad confidence limits. Goldman perimetry cannot be carried out reliably in very young children but the visual-evoked potential technique developed by Harding *et al*. [13] can be used in children with a developmental age as low as 2 or 3 years. Evidence for retinal abnormities from infancy can be obtained using electroretinography (ERG) [14].

With regard to the minimum time of treatment resulting in VFDs, using data made available to them from Ovation Pharmaceuticals (not available to the current author), Willmore *et al.* [2] stated that the earliest onset of a first abnormal visual field examination in children was 11 months, with a mean time to onset of 5.5 years, and in infants, the earliest sustained onset of a retinal defect was 3.1 months. Studies on the minimum dose required to produce VFDs have generally been performed in adults and have not reached consistent conclusions, although Kalviainen and Nousiainen [15] have stated that the risk increases with cumulative exposure, increasing in the first two years and first 2kg of intake and stabilising after three years and a total dose of 3kg.

Although the recommendation is that sequential visual field testing be performed, it is not clear whether stopping the VGB after VFDs have been detected will minimize any damage. Some studies have suggested that the abnormalities are reversible and others have not (see earlier). Data from specific studies in infants could be of great value.

Some epileptologists predicted that early effective treatment of infantile spasms would affect the prognosis in a major way. This prediction appears to have been supported by the work of Jambaque *et al*., [16] who showed that children with infantile spasms and tuberous sclerosis,

whose spasms came under control with VGB, showed significant increases in mental score. Their behaviour also improved, although most of them continued to have partial seizures. There is a strong argument for advocating prompt, effective treatment.

Although many treatments have been tried, the two that have been shown consistently to be of benefit are VGB and ACTH/steroids [10]. For babies with infantile spasms secondary to tuberous sclerosis, most clinicians would advocate VGB as first-line treatment, because of the high probability of a good response. The aim of the UKISS study [10] was specifically to compare these two treatments for infantile spasms in those who did not have tuberous sclerosis. ACTH/steroids appeared to be superior, although with longer periods of treatment there has been a suggestion that VGB might be as good. Apart from the VFDs, VGB is usually well tolerated. This has led to the suggestion that it might be tried first and, if a satisfactory response is not achieved after two weeks, then the treatment should be changed to ACTH or steroids [17].

With regard to the recommended duration of treatment of infantile spasms, there is a considerable variation in practice. Although, the limited evidence available suggests that the risk of VFDs is low in children who were treated, as infants, with VGB for infantile spasms [12], it might seem wise to treat with the minimum dose and duration, to reduce the possible risk. Again, clear unequivocal data is still required.

What conclusions can be drawn and what recommendations should be made? The largest dataset indicates that visual field defects result from prolonged VGB treatment in about 25% of adults and 15% of children [2]. Although they are asymptomatic in the majority of patients, sometimes the field restriction is severe and VFDs may result in significant disability, for example in preventing driving or affecting sports that depend on good peripheral vision. For the treatment of resistant partial-onset seizures, the advantages and disadvantages need to be discussed openly with patients and the recommendation is for serial VFD testing. For babies treated with VGB for infantile spasms, the situation is less clear. VGB almost certainly should be the first-line treatment if the spasms are secondary to tuberous sclerosis. In other cases, a time-limited trial of VGB might be advocated and if there is no satisfactory response, the treatment should be changed to ACTH/steroids. Although the risk for VFDs seems to be low in children who were treated with VGB for infantile spasms in the first two years of life, the evidence remains sparse and the treatment should not be continued for any longer than necessary.

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