SHORT REPORT

The legacy of vigabatrin in a regional epilepsy clinic

A Nicolson, J P Leach, D W Chadwick, D F Smith

J Neurol Neurosurg Psychiatry 2002;**73**:327–329

Objectives: To review all patients who had received vigabatrin at the Walton Centre to determine the incidence of visual field defect, seizure outcome if vigabatrin had been stopped, and adherence to guidelines on the use of vigabatrin in clinical practice.

Methods: Retrospective review of 583 patients prescribed vigabatrin at any time between 1989 and 2001 from a regional and satellite epilepsy clinic. Data were collected on dose and duration of treatment, results of quantitative perimetry, and reasons for, and outcome of, discontinuation.

Results: The visual fields were abnormal with no alternative cause in 42 of the 98 tested (43%). There was no clear relation between the cumulative dose of vigabatrin received and the occurrence of a visual field abnormality. Fifty patients continued taking vigabatrin, and a further 84 were lost to follow up while taking vigabatrin. In 75 patients who had stopped vigabatrin due to a visual field abnormality or concern over this potential adverse effect, the seizure control was no different or had improved in 66 (88%), while it had deteriorated in only 7 (9%).

Conclusions: This study confirms the previously reported high incidence of asymptomatic visual field defects associated with vigabatrin. Many patients taking vigabatrin may not have been counselled about the risks, and there are significant cost implications in tracing and assessing those patients lost to follow up. Switching over to another antiepileptic drug usually does not result in deterioration in seizure control, but in clinical practice an individual risk to benefit ratio needs to be taken into consideration.

Vigabatrin was the first novel antiepileptic drug (AED) to receive a product licence in the United Kingdom. As the first new drug to be licensed since valproate and having proven efficacy in refractory partial and tonic-clonic seizures,[1] it was widely prescribed to patients with drug resistant partial epilepsies. The first reports of severe symptomatic visual field constriction appeared in 1997[2 3] and it later became clear that asymptomatic, characteristically binasal visual field defects (VFDs) were common in patients taking vigabatrin.[4–9] It is generally believed that the VFDs are irreversible[6 10–12] and worsen with continued treatment,[8] but reports have suggested that they can remain stable.[13] Occasionally, VFDs may improve on cessation of vigabatrin.[14 15]

Guidelines have been published on the use of vigabatrin, both generally[16] and more specifically in children.[17] These guidelines advise that all patients taking the drug should be assessed for continuing need and in those who continue treatment, six monthly quantitative visual field perimetry should be carried out. We have analysed data from all of the patients who received vigabatrin at the Walton Centre, with the aim of assessing our adherence to these guidelines, the visual field results in those tested, and the seizure outcome in those patients who had stopped taking vigabatrin.

METHODS

Patient data were recorded prospectively on a computerised database during the study period. From this database, 583 patients were identified as having received vigabatrin at the Mersey Regional Epilepsy Clinic and at a satellite clinic at any time between 1989 and 2001. For patients who continued to receive vigabatrin we recorded whether they had been counselled of the risk for VFD and whether the continuing need for vigabatrin had been assessed. In those who had discontinued vigabatrin, subsequent seizure control was noted for at least a six month period following its cessation. Seizure control was defined as having "no change" if the epilepsy control was similar to that before the study, as "better" if there was a clear documented improvement, and as "worse" if seizures were either more severe or more frequent.

The results of visual field analyses, using standard Humphrey perimetry in each case, were noted together with dose of vigabatrin received over time. A VFD with no identifiable cause other than vigabatrin was considered to be related to the drug. Patients in whom visual field analysis should have been considered were those taking vigabatrin after January 1998 under regular follow up and had taken vigabatrin for more than one year.

RESULTS

In the group of 583 patients (299 female, 284 male patients), 535 had partial epilepsy and 38 had generalised epilepsy. Most of the latter group had started taking vigabatrin in the early years of its use and were treated for a short period. It became apparent that eight had non-epileptic attack disorder and two had syncope.

Visual field results

The visual fields were tested in 98 (57%) of the 172 patients in whom it was felt that analysis should have been considered. This figure is relatively low because testing was felt to be unnecessary in asymptomatic patients in whom vigabatrin was to be electively stopped. Non-attendance and poor compliance with visual field testing were also contributing factors. Visual fields were normal in 34 (35%) and abnormal in 64 (65%); in 42 (43%) there was no identifiable cause other than exposure to vigabatrin. In the other 22 the most common causes of abnormality were intracerebral lesions, stroke, and previous surgery or trauma. Only one patient with a vigabatrin related VFD was symptomatic and another three patients noted vague visual symptoms thought unlikely to be related to the VFD. There was no significant trend for a positive relation between cumulative dose of vigabatrin and the occurrence of a VFD ($p > 0.5$; table 1). Forty nine per cent of males tested had a vigabatrin related VFD (odds ratio 1.58, 95% confidence interval 0.70 to 3.59), compared with 38% of females (odds ratio 0.63, 95% confidence interval 0.29 to 1.33).

Abbreviations: AED, antiepileptic drug; VFD, visual field defect

Table 1 Number of VFDs depending on cumulative dose of vigabatrin received (daily dose × number of days treated)

Total vigabatrin dose (kg)	Range	Number of patients tested	Number of vigabatrin VFDs (%)
<2	0.09–1.96	10	3 (30)
2–4	2.01–3.95	28	12 (43)
4–6	4.02–5.56	24	10 (42)
6–10	6.03–8.52	21	9 (43)
>10	10.22–19.72	15	8 (53)

$\chi^2 = 1.359$, four df ($p > 0.5$). VFDs, visual field defects on testing from any cause; Vigabatrin VFDs, visual field defects that the examining ophthalmologist felt likely to be due to vigabatrin.

Treatment issues

Four hundred and forty five (76%) patients had stopped vigabatrin and 50 (9%) continued treatment. There was uncertainty in 84 (14%) because they had been lost to follow up while taking vigabatrin. All of the patients who continued taking vigabatrin were counselled about and assessed for continuing need and in 43 (86%) a sustained benefit was evident. Of the patients who continued taking vigabatrin, 7 (14%) were seizure free and, interestingly, 11 (13%) of the patients lost to follow up while taking vigabatrin were also in remission at the last appointment.

Of those who stopped vigabatrin for all reasons, 416 (93%) experienced either an improvement in seizure control or no change. Seizure control deteriorated in only 22 (5%). When the group of most interest was analysed, similar results were found and seizure outcome was also good. Among those who stopped taking vigabatrin because of a VFD or the potential risk of VFD (n = 75, all with partial epilepsy), only 7 patients (9%) experienced any deterioration in seizure control compared with 29 (39%) who were better and 37 (49%) unchanged. The outcome was better when vigabatrin was substituted by an alternative AED, with only 2 of 46 patients (4%) experiencing a worsening of seizure control and 28 (61%) improving.

DISCUSSION

This study confirms the high incidence of asymptomatic VFD in patients taking vigabatrin, with 43% of the population tested being affected. This result correlates well with findings of previous studies.[5–8] In our group of patients there was no clear relation between the cumulative dose of vigabatrin and the occurrence of a VFD, although those with the largest cumulative dose (> 5 kg) had a slightly higher incidence. There is some evidence of such a link[7 12 18–20] but there are clearly patients in whom low cumulative doses can lead to VFD, and in others there is no evidence of VFD even after a high cumulative dose. There has also been the suggestion that male sex increases the risk of VFD by up to twofold,[20] and we found an increased incidence in male patients tested. These findings suggest that genetic factors may contribute to the development of VFD. If it were possible to identify patients who are at lower risk of vigabatrin related VFD it would have implications in paediatric practice, especially in the treatment of infantile spasms for which vigabatrin is considered first line treatment in the United Kingdom.[21 22] This is particularly so because reliable quantitative visual field perimetry is very difficult below the age of nine years and in the presence of other neurological deficits.

When vigabatrin was licensed in the United Kingdom in 1989 it was the first new AED to emerge since valproate in the 1970s. There was therefore a large population of patients with drug refractory epilepsy for whom this new drug held great promise, and so it was widely prescribed. Many who were treated before the risk of VFD became apparent would no longer be under the follow up of a specialist clinic, particularly if they responded well to vigabatrin. This is shown in our group with remission rates similar in those lost to follow up and in those under regular review. This patient group is of particular concern to us, as they may still be taking vigabatrin and be unaware of the high risk of VFD. The duty of care is shared between the clinic and the general practitioner, and when such a group is identified it is our responsibility to endeavour to trace and reassess them. In our centre we are contacting such patients, through either general practitioner records or a regional NHS database, and offering a further assessment to those continuing treatment with vigabatrin.

The issue of treatment with vigabatrin has both safety and financial implications, and it is essential that its use be audited within specialist epilepsy centres. However, the main concern for patients whose seizures are well controlled by vigabatrin is the risk of deterioration in seizure control on electively stopping treatment. A recently published study showed the seizure outcome to be good in patients switched to an alternative AED[13] but this was limited by the small numbers involved. Our study provides information from large numbers of patients that the seizure outcome is generally good on cessation of vigabatrin.

Since 1989 there has been a huge expansion of available AEDs, some of which these patients would not have been exposed to, and so our treatment options are generally wider than when vigabatrin was introduced. If we also consider the high risk of VFD and the cost implications of patients continuing to take vigabatrin, there is a strong argument that most patients should stop treatment. However, we would argue that there is an individual risk to benefit ratio that needs to be considered, and there are clearly some circumstances in which patients would elect to continue taking vigabatrin. In some cases of drug refractory epilepsy, vigabatrin can be very effective and this needs to be considered when discussing cessation.[23]

Conclusion

Vigabatrin is an effective AED in the treatment of refractory partial epilepsy and infantile spasms but carries a high risk of VFDs. Appropriate counselling and monitoring therefore are vital; however, in many cases this is not achieved, usually because of loss to follow up in specialist clinics. The seizure outcome in those who choose to stop vigabatrin is generally good but there may be patients at low risk of VFDs in whom it is appropriate to continue treatment. Identifying genetic factors would guide us as to which patients are at low risk. This would lead to safer prescribing of this drug and would have particular implications for paediatric practice.

Authors' affiliations

A Nicolson, J P Leach, D W Chadwick, D F Smith, The Walton Centre for Neurology and Neurosurgery, Lower Lane, Fazakerley, Liverpool, L9 7LJ, UK

Competing interests: none declared

Correspondence to: Dr A Nicolson, The University Department of Neurosciences, Clinical Sciences Centre for Research and Education, Lower Lane, Fazakerley, Liverpool L9 7LJ, UK; andrew@nicolson71.freeserve.co.uk

Received 25 February 2002
In revised form 2 May 2002
Accepted 30 May 2002

REFERENCES

1 **Marson AG**, Kadir ZA, Hutton JL, *et al*. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia* 1997;**38**:859–80.
2 **Eke T**, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997;**314**:180–1.

3 **Harding GE**. Severe persistent visual constriction associated with vigabatrin. *BMJ* 1998;**315**:232–3.
4 **MacKenzie R**, Klistorner A. Asymptomatic as well as symptomatic defects occur with vigabatrin. *BMJ* 1998;**316**:233.
5 **Kalviainen R**, Nousiainen I, Mantyyjarvi M, *et al*. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. *Neurology* 1999;**53**:922–6.
6 **Wild JM**, Martinez C, Reinshagen G, *et al*. Characteristics of a unique visual field defect attributed to vigabatrin. *Epilepsia* 1999;**40**:1784–94.
7 **Lawden MC**, Eke T, Degg C, *et al*. Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999;**67**:716–22.
8 **Hardus P**, Verduin WM, Postma G, *et al*. Concentric contraction of the visual field in patients with temporal lobe epilepsy and its association with the use of vigabatrin medication. *Epilepsia* 2000;**41**:581–7.
9 **Gross-Tsur V**, Banin E, Shahar E, *et al*. Visual impairment in children with epilepsy treated with vigabatrin. *Ann Neurol* 2000;**48**:60–4.
10 **Lhatoo SD**, Sander JWAS. Infantile spasms and vigabatrin: visual field defects may be permanent. *BMJ* 1999;**318**:57.
11 **Johnson MA**, Krauss GL, Miller NR, *et al*. Visual function loss from vigabatrin: effect of stopping the drug. *Neurology* 2000;**55**:40–5.
12 **Malmgren K**, Ben-Menachem E, Frisen L. Vigabatrin visual toxicity: evolution and dose dependence. *Epilepsia* 2001;**42**:609–15.
13 **Paul SR**, Krauss GL, Miller NR, *et al*. Visual function is stable in patients who continue long-term vigabatrin therapy: implications for clinical decision making. *Epilepsia* 2001;**42**:525–30.
14 **Krakow K**, Polizzi G, Riordan-Eva P, *et al*. Recovery of visual field constriction following discontinuation of vigabatrin. *Seizure* 2000;**9**:287–90.
15 **Giordano L**, Valseriati D, Vignoli A, *et al*. Another case of reversibility of visual-field defect induced by vigabatrin monotherapy: is young age a favourable factor? *Neurol Sci* 2000;**21**:185–6.
16 **Stonier PD**. *Important new information on Sabril (vigabatrin)*. Hoechst Marion Roussel, Uxbridge, UK. Personal correspondence, 27 August 1999.
17 **Vigabatrin Paediatric Advisory Group**. Guideline for prescribing vigabatrin in children has been revised. *BMJ* 2000;**320**:1404–5.
18 **Hardus P**, Verduin WM, Engelsman M, *et al*. Visual field loss associated with vigabatrin: quantification and relation to dosage. *Epilepsia* 2001;**42**:262–7.
19 **Toggweiler S**, Wieser HG. Concentric visual field restriction under vigabatrin therapy: extent depends on the duration of drug intake. *Seizure* 2001;**10**:420–3.
20 **Kalviainen R**, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. *CNS Drugs* 2001;**15**:217–30.
21 **Appleton RE**. The role of vigabatrin in the management of infantile epileptic syndromes. *Neurology* 1993;**43**:S21–3.
22 **Cossette P**, Rivello JJ, Carmant L. ACTH versus vigabatrin theray in infantile spasms: a retrospective study. *Neurology* 1999;**52**:1691–4.
23 **Sankar R**, Wasterlain CG. Is the devil we know the lesser of two evils? Vigabatrin and visual fields. *Neurology* 1999;**52**:1537–8.