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SHORT REPORT

Evaluation of vigabatrin as an add-on drug in the management of severe epilepsy

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Abstract

The effects of the addition of Vigabatrin, a new anti-epileptic drug, to the therapy of 128 patients with severe medically refractory epilepsy is reported. Forty two (33%) of patients experienced side effects, which were predominantly neurotropic. In 28 (22%), the drug was withdrawn because of these side effects. The commonest side effects were drowsiness and behavioural change. The remaining 100 patients were followed for a mean of 30 weeks (range 12–75). Forty one of these patients showed a marked improvement in seizure frequency (a 50% or more reduction when compared with the pre-trial period), and nine (7%) were rendered seizure free. Apparent tolerance to the effects of the drug were noted in five patients. An exacerbation of seizures may occur if the drug is withdrawn too quickly. Vigabatrin appears to be a promising new anti-epileptic drug.

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Vigabatrin (GVG) is an irreversible inhibitor of gamma-aminobutyric acid aminotransferase (GABA-T), the principal catabolic enzyme of the cerebral inhibitory neurotransmitter GABA. The effect of GVG is to considerably increase GABA concentrations in the brain.[1–3] This is believed to be the basis of its anti-epileptic action. The efficacy of GVG as a new anti-epileptic drug has been shown in several controlled studies and it has been shown to reduce partial and generalised tonic clonic seizures.[4–9]

One of the main concerns about the clinical usage of GVG is that in early toxicity studies in experimental animals, micro-vacuoles were seen in the myelin of certain areas of the brain after chronic administration of large doses of GVG. These were subsequently identified as intra-myelinic oedema, and were reversible on cessation of GVG administration. This micro-vacuolation was seen in rodents and beagles, but has not been seen in primates or in humans.[10–12] Nonetheless, careful scrutiny is still required in human subjects taking this drug.

We report here our experience with vigabatrin used in an open fashion, as an add-on drug in the management of patients with severe intractable epilepsy in tertiary referral centres.

Patients and methods

We have studied GVG as an add-on drug in 128 adult patients in an open uncontrolled clinical study during the period from September 1987 to June 1989. All patients had severe medically refractory epilepsy and were evaluated either as inpatients or outpatients at the Chalfont Centre for Epilepsy, or the National Hospitals for Nervous Diseases. All patients gave informed consent, and specific criteria for entry into the study included: four or more seizures a month in the immediate three months pre-trial period, recorded prospectively; an adequate previous trial of treatment with carbamazepine, phenytoin, phenobarbitone (or primidone) and sodium valproate in monotherapy or combination (many other drugs had also been used, and these patients were considered medically intractable cases); no systemic or active psychiatric condition; no pseudoseizures complicating the epilepsy.

Table 1 shows the clinical details of the patients. The majority (81%) had a mixed partial seizure disorder, with a mean of 2·3 seizure types per patient. Epilepsy was symptomatic in 55% of the sample, and the mean duration of the disorder was 21 years. Thirty seven patients were on monotherapy on entry, 65 were taking two and 26 were taking three concomitant anti-epileptic drugs when GVG treatment was started. The commonest con-

Table 1 Patients' details

n = 128; 67 males, 61 females.

	Mean	*Range*
Age (years)	30·2	18–58
Age of onset of seizures (years)	9·3	0–32
Duration of epilepsy (years)	21·2	3–44
Aetiology	*Patients*	*Per cent*
Birth injury	17	13%
Head trauma	13	10%
Post-infection	12	9%
Tumour	6	5%
Lennox Gastaut[1]	5	4%
Others[2]	17	14%
No cause identified	58	45%
Seizure classification		
Complex partial	2	1%
Second. Generalised	4	3%
Mixed partial	104	81%
Generalised tonic clonic	3	2%
Mixed generalised	11	9%
Unclassifiable	4	3%
One seizure type	8	6%
Two seizure types	76	60%
3 or more seizure types	44	34%

[1] = Idiopathic cases, without any specific aetiology.
[2] = History of febrile convulsion (11), vascular (2), vaccination (2), Sturge-Weber (1) and tuberous sclerosis (1).

comitant anti-epileptic drug was carbamazepine (108), followed by sodium valproate (38) and phenytoin (35).

GVG was started at a low dose (500–1000 mg/day) and was progressively increased, in weekly steps, to a maximum of 4000 mg, provided no side effects occurred. If satisfactory seizure control was achieved the dose at which this occurred was maintained. If side effects did occur the dose was reduced, unless they were severe enough to warrant the interruption of treatment. In six cases the dose was increased beyond 4000 mg because of partial improvement or the development of tolerance and the absence of side effects. After eight to 16 weeks on full treatment, an evaluation of the effectiveness of GVG was made and if there was no clear benefit treatment was tapered off.

Results

During the evaluation period any alteration in seizure type or frequency and the occurrence of any side effects were recorded by the patient, attendant, relative or guardian.

Forty two patients (33%) experienced side effects (table 2). The most common were drowsiness and behavioural disturbance. This latter effect was occasionally severe, and varied from irritability, confusion and aggressive behaviour to a frank psychotic reaction. In 28 of the patients side effects were severe enough to warrant stopping the treatment. The mean vigabatrin dose in patients withdrawn from the study due to side effects was 2400 mg (range: 1000–5000 mg). Most of the side effects occurred early in treatment, with 25 of the 28 patients withdrawing from the drug in the first 12 weeks.

Behavioural disturbance was the most frequent side effect that led to withdrawal of treatment, followed by drowsiness, deterioration in seizure control and headaches. Six of the 13 patients who had behavioural disturbance showed psychotic features, which resolved with cessation of the drug. Delusions, hallucinations and paranoia were prominent features and two of these six cases had had a previous history of psychosis, which was quiescent at the time of entry. Of the remaining seven patients, two presented with irritability, two with a confusional state and three presented with aggressive behaviour. Nine patients had a deterioration in seizure control. Three of these patients had generalised seizures with myoclonic jerks, and in each case it was the myoclonus which became more frequent; the remaining patients had complex partial seizures. Three patients presented with severe drowsiness that started within days of initiating GVG treatment and which progressed to a state of stupor. In two of these patients this was associated with peripheral circulatory vasoconstriction. All three patients recovered fully within 72 hours of stopping GVG treatment.

Of the remaining 100 patients, 41 (32%) had a significant response to GVG treatment (>50% reduction in seizure number over the follow up period (mean 30 weeks, range 12–75 weeks)), of whom nine are seizure free. Thirty eight of these patients had partial and secondarily generalised seizures and the remaining three had generalised seizures. The mean GVG dose in respondents was 3230 mg/day (range: 1000 to 5500 mg/day). A further 24 patients (19%) elected to continue on GVG as in their subjective assessment seizures were decreased or less severe. Thirty patients had no response to GVG and their treatment was tapered off. Five patients who had an initial excellent response to GVG subsequently reverted to their previous pattern despite successive increase in the dose. This was observed after a mean of 48 weeks of treatment (range 32–68 weeks) and in these patients the mean dose was 5400 mg/day with a range of 4000 to 8000 mg/day. These patients also subsequently had their treatment tapered off.

Table 2 Observed side effects

	Total patient sample		*Patients withdrawn due to side effects*	
Side effect	*n = 128*	*%*	*n = 28*	*%*
Drowsiness	22	17	12	43
Behavioural disturbance	19	15	13	46
Headaches	11	9	8	28
Ataxia	10	8	6	21
Increased seizures	9	7	9	32
Periph circ shutdown	2	2	2	7
Nausea	1	1	0	0
Weight gain	1	1	0	0
Total*	42		28	

*Patients may have experienced more than 1 side effect.

Discussion

This study has an open label uncontrolled design, and as such has certain well known disadvantages. However, we consider that a study of a large number of patients, by a single experienced group in one centre has an important role in deciding the relative place of a new treatment for a condition such as epilepsy, both from the points of view of efficacy and toxicity.

A useful objective effect (defined as a 50% or more reduction in seizure frequency) was observed in 41 patients (32%), of whom nine (7%) were rendered seizure free. Most patients had partial and secondarily generalised seizures, and these seizure types seemed to respond particularly well, but as other seizure types were less represented this impression might be due to sample bias. No other differences in response were noted in other patient variables. The patients studied had severe medically refractory epilepsy, and were a severe test for any new anti-epileptic drug. A response rate of more than 50% seizure reduction in 32% of patients is a gratifying result, and there seems no doubt that this drug has a marked anti-epileptic action.

Side effects were seen in 42 patients (33%). The majority of them developed early in treatment, and neurotropic effects (for example, behavioural disturbance, drowsiness, headaches and ataxia) were the commonest reported. The most striking toxic effects were on behaviour. Behavioural disturbance ranged from irritability to psychotic reactions, and did

not seem to be dose related. Psychotic reactions were seen in six patients and in all cases resolved when GVG was discontinued. The behavioural changes in a small number of patients were severe, and this should be kept in mind when initiating GVG therapy. We are now very cautious when starting this drug in patients with a previous history of psychotic symptoms and we feel that the behaviour of all patients should be carefully monitored in the early stages of GVG treatment. Drowsiness, headaches and ataxia were usually short lived and improved without any intervention although in some patients they seemed to be dose related and abated only with a reduction in the dose of GVG. In three patients, however, drowsiness was severe enough to warrant treatment being withdrawn in its early stages.

Tolerance to the beneficial effect of GVG developed in five patients who had an excellent initial response and the full extent of this problem will only be elucidated with long term follow up.

Caution is also needed when withdrawing vigabatrin, as we have observed a severe exacerbation of seizures in patients in whom the drug was withdrawn too fast. Our current regime is to withdraw the drug incrementally each seven or 14 days.

It seems clear that GVG may be useful in controlling seizures in a number of patients with severe partial epilepsy.

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