Br. J. clin. Pharmac. (1989), **27**, 109S–112S

Vigabatrin in the treatment of epilepsy in children

J. H. LIVINGSTON[1], D. BEAUMONT[2], A. ARZIMANOGLOU[1] & J. AICARDI[1]
[1]Hopital Necker – Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France and [2]Medical Research Unit, Merrell Dow Research Institute, 56, Allée de la Robertsau, 67000 Strasbourg, France

1 This study presents the results of the preliminary screening of vigabatrin as add-on therapy in an open, non-controlled multicentre study in children with refractory epilepsy.
2 There were 135 children, with an age range of 2 months–12 years. Main seizure type was partial in 42%, generalized in 29%, Lennox-Gastaut syndrome in 19% and West syndrome in 10%.
3 Vigabatrin was added onto current antiepileptic treatment in an initially recommended dose of 40–80 mg kg^{-1} day^{-1}. However, the doses were frequently increased when tolerance allowed it, and the final mean dose used was 87 mg kg^{-1} day^{-1} (27–600).
4 A 75% to 100% reduction in seizure frequency was observed in 25% of patients (11 patients became seizure free) and 50 to 75% decrease in a further 13%. Efficacy was better in partial seizures, with good to excellent results in 49% of patients. The use of high doses, above 100 mg kg^{-1} day^{-1}, was not associated with greater efficacy in this preliminary study.
5 No side effects were reported in 79% of patients. Agitation and insomnia were observed in 8.8% and somnolence in 6%. Other adverse events included ataxia (2.2%), nausea (2.2%) and increased appetite (1%). A moderate and transient decrease in haemoglobin was reported in six patients from the same centre; these patients were all receiving very high doses of vigabatrin (250 to 600 mg kg^{-1} day^{-1}).
6 Vigabatrin thus appears to be a safe antiepileptic drug that may be effective in the treatment of severe epilepsy in children.

Keywords intractable epilepsy children vigabatrin

Introduction

Epilepsy in childhood is more common that at any other period of life. For most children, epilepsy is readily controlled with current anticonvulsant treatment and they are able to lead a normal life. However, in a sizeable minority of from 20–30% of cases (Brorson & Wranne, 1987), the seizures are not controllable by current treatments, with subsequent severe disruption to their lives, interference with learning, emotional, behavioural and school problems and the risk of prolonged seizures. This group of intractable epilepsies is heterogeneous, comprising patients with complex partial seizures, Lennox-Gastaut syndrome, myoclonic epilepsies, West syndrome and other mixed and unclassifiable seizure disorders. For a small proportion of these children surgical therapy may be effective. However, the role of surgical therapy has not yet been fully evaluated in children and there are undoubtedly many children for whom surgical intervention is inappropriate. There is thus a clear need for new, safe and effective antiepileptic drugs for the treatment of severe epilepsy in childhood.

Correspondence: Dr J. Aicardi, Hôpital Necker – Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France

Vigabatrin, whose pharmacological actions have been reviewed elsewhere in this supplement (Gram *et al.*, 1989; Schechter, 1989), is a novel anti-epileptic drug that has been extensively evaluated in adults (Browne *et al.*, 1987; Mumford & Dam, 1989). It is particularly effective as an anti-convulsant against refractory partial seizures. We report here the preliminary experience with vigabatrin in the treatment of 135 children with drug-resistant epilepsy. This study was an open preliminary assessment of the safety and efficacy of vigabatrin in a large heterogeneous group of children with drug-resistant epilepsies.

Methods

There were 135 children from 11 centres, 85 males and 50 females aged from 2 months to 12 years (mean 7.1 years). The ages were relatively evenly spread throughout childhood. All patients had drug-resistant epilepsy, with a pre-vigabatrin seizure frequency ranging from 2/month to greater than 40/day.

Seizures were classified using to the classification suggested by the International League Against Epilepsy (1981). Where the patient had a combination of seizures types and clinical features that fulfilled the criteria for diagnosis as West or Lennox-Gastaut syndrome (ILAE, 1985), they were classified accordingly (Table 1). Overall, 42% had partial seizures, 29% generalized seizures, 19% the Lennox-Gastaut syndrome, 10% West syndrome and 18 patients had unclassifiable seizures. All patients were on other anti-epileptic drugs at the time of starting treatment with vigabatrin. At the time of reporting, patients were on a mean of two other antiepileptic drugs with a range of 1 to 6. Vigabatrin monotherapy was achieved in 11 patients after progressive withdrawal of other drugs.

Table 1 Classification of seizures and epileptic syndromes

Seizure type	*Number of patients*
Partial seizures	57 (42%)
Simple partial	7
Complex partial	20
Secondarily generalized	24
Unclassified partial seizures	6
Generalized seizures	39 (29%)
Simple absences	2
Atypical absences	4
Myoclonic	10
Tonic	6
Tonic clonic	5
Unclassified generalized seizures	12
Epileptic syndromes	
Lennox-Gastaut	26 (19%)
West Syndrome	13 (10%)

This was an open, add-on non-controlled study. The initially recommended dose was 40–80 mg kg^{-1} day^{-1} but the dose was flexible according to efficacy and tolerability and finally, the mean dose used was 87 mg kg^{-1} day^{-1}. In one centre, doses of 250–600 mg kg^{-1} day^{-1} were used in six patients. Response was recorded as percentage change in seizure frequency compared with pre-vigabatrin baseline, and overall judgment of efficacy. Haematology, blood chemistry and liver function tests were monitored routinely.

Results

At the time or reporting, 39 patients continue to take vigabatrin and 34 have had more than 2 year's exposure (maximum 3 years). In 96 patients, vigabatrin was discontinued. In 71 (74%) of these, this was because of lack of efficacy. Twenty-three (24%) patients dropped out for reasons unrelated to vigabatrin. These included being lost to follow-up, poor compliance or administrative reasons. Two patients discontinued the drug because of adverse events.

Efficacy

A 75–100% decrease in seizure frequency was observed in 30 (25%) cases, with 11 of them becoming seizure free. A further 15 (13%) had a 50–75% decrease in seizure frequency.

Overall efficacy was rated as excellent in 27 (21%) cases, good in 19 (15%), moderate in 12 (9%), little or transient in 28 (22%), nil in 34 (26%), with 9 (7%) patients becoming worse. Efficacy was better in partial seizures, with good to excellent results in 49% of patients (Figure 1) as compared with 24% of patients with generalized seizures. In 34 patients with more than 6 months' exposure to vigabatrin and a quantified change in seizure frequency from baseline, there was no correlation between dose and percentage of seizure reduction.

Tolerability

No adverse reactions were observed in 107 patients (79%). The remaining 28 patients experienced a wide range of adverse effects (Table 2). These were rated as severe in only seven patients. Agitation and insomnia were observed in 8.8%, somnolence in 6%. These

effects were mostly transient or responded to a decrease in dose.

In four patients, vigabatrin was stopped because of severe side effects. In two of these patients side effects persisted after vigabatrin was stopped. Thus overall, adverse reactions (severe agitation) unequivocably related to vigabatrin accounted for 2% (2/96) of dropouts.

In six patients a moderate decrease in haemoblobin concentration (2.5 g/100 ml on average) was noted. This returned to normal after decrease in the dose or discontinuation of vigabatrin. However, in one patient the haemoglobin returned to normal with no change in the dose. All these patients were from the same centre, and were receiving very high doses of vigabatrin (250–600 mg kg^{-1} day^{-1}). No other changes in haematological or biochemical parameters have been demonstrated.

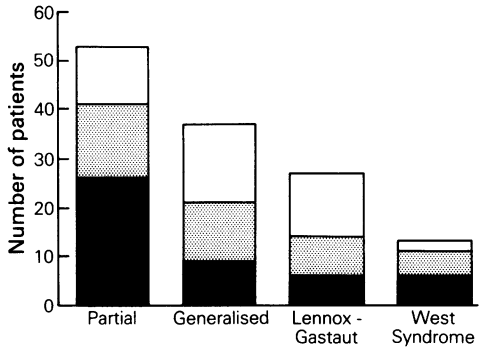

Figure 1 Efficacy of vigabatrin according to seizure type. □ none to worsening, ⊡ little to moderate, ■ good to excellent.

Discussion

These preliminary results suggest that vigabatrin is an effective and safe antiepileptic drug in children with severe epilepsy. The overall efficacy figures are lower than those reported from adult studies (Browne *et al.*, 1987; Loiseau *et al.*, 1986; Gram *et al.*, 1985) where up to 50% of patients in most studies had a 50–100% reduction in seizure frequency. This difference in efficacy is not surprising when one considers the heterogenous nature of intractable epilepsy in childhood, where many patients have the Lennox-Gastaut syndrome, West syndrome or unclassifiable or mixed epilepsies. In adult series the majority of patients with intractable epilepsy have complex partial seizures (Dam, 1986). In this study the number of patients with partial seizures having a good to excellent response (49%) approached that of adult studies.

In the severe generalized epilepsies of infancy such as the myoclonic epilepsies and the Lennox-Gastaut syndrome, the results are much less impressive. However, some of these patients have had good to excellent responses.

Although this study was not aimed at determining response to different doses of vigabatrin, there did not appear to be any clear dose-response relationship and thus no obvious increase in efficacy on higher doses. Several investigators have used higher doses than initially recommended, and despite this, tolerability has continued to be excellent. Dose finding studies are currently in progress.

In agreement with adult studies, tolerance of vigabatrin appears excellent, with the side effects of somnolence, agitation and insomnia being the most common. Agitation was probably more common in children than adults. In many patients who did have side effects, these were transient

Table 2 Adverse effects due to vigabatrin in 135 patients (32 effects reported by 28 patients)

Adverse event	*Number of patients*	*Comments*
Excitation, agitation	9 (8.8%)	Severe in 2, transient in 7
Insomnia	3	Severe in 1
Fatigue, somnolence	8 (6%)	Severe in 3, responded to drug decrease
Ataxia	3 (2.2%)	
Nausea, vomiting	3 (2.2%)	Severe but transient in 1
Appetite increased	2 (1.5%)	
Appetite decreased	1	
Increased thirst	1	
Epigastric pain	1	
Headache	1	Severe but transient

and overall only two patients had to stop the drug because of clearly vigabatrin-related side effects. The transient and reversible decrease in haemoglobin seen in six patients from the same centre seems to be related to the very high doses of vigabatrin they were receiving.

Long-term tolerability seems to be good, with at present 34 patients having more than 1 year's exposure to vigabatrin. The longest exposure in this series is currently 4 years, with continued efficacy. Tolerance to the antiepileptic effects of vigabatrin has been observed in some children. However, results from adult studies suggest that tolerance is not a common problem and that continued long-term response is possible (Browne *et al.*, 1987).

In conclusion, vigabatrin appears to be a well-tolerated compound with a genuine antiepileptic action in the severe epilepsies of childhood, particularly against partial seizures.

We wish to thank the following investigators for their participation in the study: Drs Evrard, Jaecken, Rucquoy, Sorel (Belgium); Dam (Denmark); Dulac, Gastaut, Loiseau, Roger (France); Bechinger, Doose, Petersen, Shmitz-Moor (Germany); Perucca, Tassinari (Italy).

References

Brorson, L. O. & Wranne, L. (1987). Long term prognosis in childhood epilepsy; Survival and seizure prognosis. *Epilepsia*, **28**, 324–330.

Browne, T. R., Mattson, T. H., Penry, J. K., Smith, D. B., Treiman, D. M., Wilder, B. J., Ben-Menachem, E., Napoliello, M. J., Sherry, K. M. & Szabo, G. K. (1987). Vigabatrin for refractory complex partial seizures: Multicenter single-blind study with long term follow-up. *Neurology*, **37**, 184–189.

Dam, M. (1986). In *Intractable epilepsy*, eds. Schmidt, D. & Morselli, P. L., pp. 1–3. New York: Raven Press.

Gram, L., Klosterskov, P. & Dam, M. (1985). Gamma-vinyl-GABA: A double-blind placebo-controlled trial in partial epilepsy. *Ann. Neurol.*, **17**, 262–266.

Gram, L., Larsson, O. M., Johnsen, A. & Schousboe, A. (1989). Experimental studies on the influence of vigabatrin on the GABA system. *Br. J. clin. Pharmac.*, **27**, 13S–17S.

Loiseau, P., Hardenberg, J. P., Pestre, M., Guyot, M., Schechter, P. J. & Tell, G. P. (1986). Double-blind placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug resistant epilepsy. *Epilepsia*, **27**, 115–120.

Mumford, J. P. & Dam, M. (1989). Meta-analysis of European placebo controlled studies of vigabatrin in drug resistant epilepsy. *Br. J. clin. Pharmac.*, **27**, 101S–107S.

Schechter, P. J. (1989). Clinical pharmacology of vigabatrin. *Br. J. clin. Pharmac.*, **27**, 19S–22S.