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Efficacy and safety of vigabatrin in the long-term treatment of refractory epilepsy

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1 The long term safety and efficacy of vigabatrin has been studied in 254 patients with refractory epilepsy (82% with partial seizures) in 23 different clinics in eight European countries.

2 This was an open multicentre study in which patients who had experienced a significant benefit from vigabatrin and had continued to take the drug for 1 year or longer were eligible for evaluation. The mean duration of therapy in the 254 patients was 22.7 months; 72 patients received vigabatrin for more than 2 years.

3 Patients were severely affected by epilepsy with a median monthly seizure frequency of 15.7 despite taking an average of 2.2 antiepileptic drugs. On vigabatrin, the median seizure frequency was about 35% of baseline, remaining stable over time despite a 10% reduction in the number of concurrent medications.

4 The lack of tachyphylaxis to the antiepileptic effect of vigabatrin is shown by the small number of patients who discontinued for insufficient efficacy (11%), two thirds of them during the first 6 months of follow-up. Maintenance of efficacy is also clearly demonstrated by analysis of 2 year and 3 year cohorts of patients.

5 Clinical and biological tolerability was excellent. There was a very low rate of drop out for adverse events (1.6%). Adverse events, mainly sedation, irritation and weight gain were mostly mild and transient. 75% of patients reported no adverse event at all.

6 Safety evaluation included serial neurological, ophthalmological and general examinations : no new abnormal clinical feature or adverse event emerged with long term therapy.

Keywords vigabatrin efficacy safety refractory epilepsy

Introduction

Vigabatrin increases the concentration of GABA in the brain and CSF, and has been shown to be a very effective therapy in patients with refractory epilepsy in a series of double-blind studies (Mumford & Dam, 1989). However proper clinical assessment of a new anticonvulsant must include long term monitoring of safety and efficacy over a period in excess of 12 months, in addition to short-term controlled studies.

During the pre-clinical testing of vigabatrin, reversible intramyelinic oedema was observed in white matter tracts of the brains of certain animal species (Butler *et al.*, 1987), though no such changes were found in the peripheral nervous system. This finding increased the importance of monitoring patients treated with vigabatrin for prolonged periods of time.

The purpose of this study was to examine the long-term safety and efficacy of vigabatrin as

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Table 1 Distribution of patients and centres by country

Country	*Number of centres*	*Number of patients*
Belgium	1	10
Denmark	1	30
Finland	1	52
France	12	96
Germany	2	18
Holland	1	6
Italy	4	34
Sweden	1	8
Total	23	254

add-on treatment for drug-resistant epilepsy in patients treated in Europe for over one year.

Methods

This was an open multicentre study in which patients who had continued to take vigabatrin for 1 year or longer were eligible for evaluation. These patients were commenced on vigabatrin treatment in a variety of different protocols and, because of a favourable response to the drug, were subsequently continued on vigabatrin and carefully monitored to document control of seizures, vigabatrin adverse events, laboratory tests and physical examination.

A total of 23 epilepsy centres in eight European countries recruited 254 patients (Table 1). Thirty-six patients had started vigabatrin on a double-blind cross-over study *vs* placebo, 76 on a single-blind placebo-controlled study, 52 on a double-blind dose-reduction study and 62 on an open study. The remaining 28 patients had started vigabatrin on an open named-patient basis.

There were 141 males (55.5%) and 113 females, with a mean age of 28 years (range 1–69). Age was less than 16 years in 37 patients. The majority of patients (84.5%) were monitored in an out-patient clinic; 28% were employed at the time of the study and 9% were students or school children.

The majority of patients (82%) had partial epilepsies presenting with simple and/or complex partial seizures, 45% with secondary generalisation. Only 15% of adult patients had generalised types of epilepsy, as opposed to 50% of children under 16 years.

Seizure frequency before vigabatrin—during placebo periods in case of a previous controlled study—varied between 1.5 and more than 1000 per month (median 15.7), in spite of an average of 2.2 antiepileptic drugs (at optimal dose) per patient. The most commonly used drug was carbamazepine, taken by 69% of patients, followed by phenobarbitone (38%).

Each patient had a full evaluation at 3 monthly intervals or more frequently. Seizure frequency was recorded by the clinical investigator based on the patient's seizure calendar. Patients were examined and data recorded under four different headings: general examination, neurological examination, psychological examination and ophthalmological examination. The latter were performed only 6 monthly. At each visit the investigator recorded the description, date of onset, severity, and relationship to vigabatrin of all adverse events reported by the patient. Routine haematological and clinical chemistry analyses were performed prior to vigabatrin and at 3 monthly intervals. Special clinical examinations were performed in certain centers, e.g. evoked potential recordings, and these are the subjects of separate publications (Liegois-Chauvel *et al.*, 1989; Cosi *et al.*, 1988).

Results

Exposure to vigabatrin

The mean (± s.d.) daily dose of vigabatrin was 3.1 ± 1.3 g or 52.5 ± 30.8 mg kg^{-1} body weight. There was a wide range of doses, from 0.5 g up to 9.0 g day^{-1}. All 254 patients were followed for at least 12 months on vigabatrin. Some 36 were treated for 36 months or longer and 72 for 24 months or longer. The mean duration of therapy in the 254 patients was 22.7 months ± 11.4 (mean ± s.d.).

Reasons for discontinuation

Fifty-four patients (21.3%) discontinued vigabatrin after having received the drug over 12 months. Twenty-six patients out of 254 (10.2%) dropped out for insufficient efficacy on long

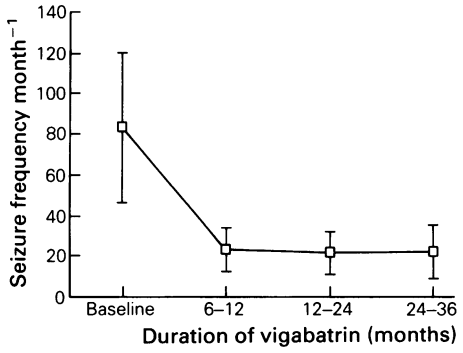

Figure 1 Three year cohort analysis of total seizure frequency: 28 patients, mean ± s.e. mean.

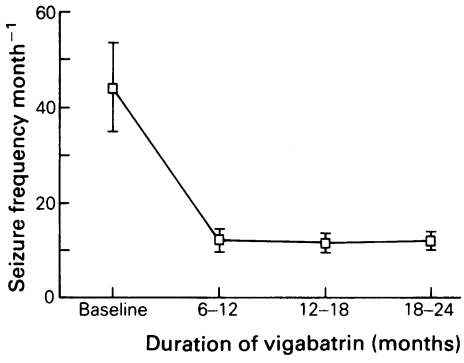

Figure 2 Two year cohort analysis of total seizure frequency: 85 patients, mean ± s.e. mean.

term treatment, 18 of them during the first 6 months of follow-up. Adverse event was the main cause of discontinuation in only four patients (1.6%) and an additional reason to lack of efficacy in three. In 17 patients, the study was discontinued for a variety of reasons not related to the study drug, and four patients died in the course of the study. None of these deaths was attributed to vigabatrin by the clinical investigator. One patient died from a chronic cardiac insufficiency, one from a liver cancer. Sudden death in a third patient was attributed to a generalised seizure, while the last patient died in status following modifications of his antiepileptic therapy after surgery. In one patient, it was possible to perform a full post-mortem examination, including optic and electron microscopy of the white matter. This did not reveal any abnormalities resembling those seen in animal toxicology studies (Pedersen *et al.*, 1987).

Efficacy

When considering the total of different seizure types the median seizure frequency on vigabatrin was about 35% of pre-treatment baseline, and showed no tendency to increase with time. In these selected patients who had demonstrated a significant response to vigabatrin during earlier studies, the same continued efficacy was observed whether the patient had complex partial, secondarily generalised or primary generalised seizures. Very good long-term efficacy was also observed in the 37 children aged under 16 years.

Due to patients having different lengths of therapy, the question of long-term efficacy is best addressed by a cohort analysis: 28 patients have had documented seizure frequency at treatment periods of 6–12, 12–24, and 24–36 months (3 year cohort); 85 patients have had data at 6 month intervals, up to 24 months (2 year cohort). Results are set out in Figures 1 and 2. This analysis confirms the continued efficacy of vigabatrin therapy in the long-term.

At the last documented visit in these 254 patients, the investigator judged 83% of the patients to be well or moderately controlled while the patient himself reported that the drug helped very much, much or moderately in 81% of cases. Children did not differ from adults with respect to this final evaluation of efficacy.

Adverse events

During the study, 75% of patients reported no adverse event at all. In the other patients, the interpretation of reported adverse events must take into account the number of concomitant drugs as this add-on study. Some 32% of all adverse events were considered by the recording investigator as 'not study drug related' i.e. due to concurrent drug, concurrent illness or other known cause. Of the remaining 68% of adverse events attributed to the study drug, some 4% were attributed definitely, 35% probably and 61% possibly to vigabatrin by the investigator. Central nervous system (CNS) events appeared predominant: sedation (fatigue, somnolence) was reported by 55 out of the 254 patients (21.6%) and psychiatric events, such as irritation, aggression, memory problems by 18.5%. Weight increase was reported by 6.7% of patients. Other events were below 3% in incidence. Severity of these adverse events was mostly mild (58.2%) or moderate (31.3%), and severe in 10.5% of reports.

Four patients had vigabatrin discontinued for adverse events, namely severe psychotic reac-

tion, mild visual disturbance and constipation. A further three had lack of efficacy as the main reason and adverse event as an additional reason for discontinuation: mild vertigo, severe schizophrenic symptoms, and mild acne. Therefore, after 1 year of vigabatrin therapy, discontinuation for adverse event was very rare. Further indication that no new or severe adverse reactions emerge on long-term therapy is given by the analysis of adverse events incidence with time.

Such an analysis is set out in Figure 3, where side effects are grouped into sedation, psychiatric, neurological, digestive, nutritional and other. It clearly appears that there was a tendency for adverse events to moderate when vigabatrin was continued.

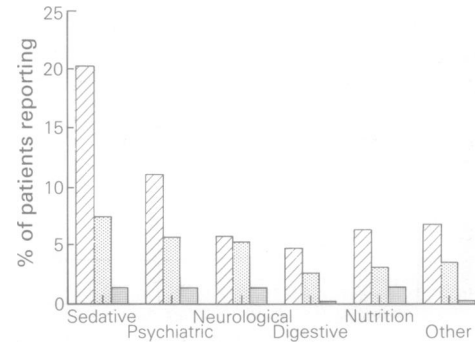

Figure 3 Incidence of adverse events with duration of vigabatrin therapy, ▨ year 1, ▩ year 2, ▩ year 3.

Clinical safety parameters

Patients were regularly examined during long-term therapy, with particular attention paid to a thorough neurological examination.

Some abnormality on neurological examination before starting vigabatrin was found in 26% of patients. The incidence of changes on vigabatrin was strikingly low (below 3% of all examinations performed) and further decreased with time. The few changes reported were transient and did not point to a drug-related neurological adverse event.

The ophthalmic examinations did not disclose any abnormality during vigabatrin, except for a non drug-related intercurrent event in four patients.

Laboratory safety tests

On the routine laboratory testings regularly performed, some changes were significant on statistical analysis: a small (4%) decrease in haemoglobin and haematocrit was observed whereas leukocytes and platelets remained unchanged. As individual values remained within normal ranges, it is not unexpected that this change has not been reported by the investigators as an adverse event.

There was some alteration in liver transaminases: a 10–20% decrease in SGOT and a 30–50% decrease in SGPT. Again, these were not reported as abnormal events by the investigators. Plasma alkaline phosphatase, creatinine and uric acid showed no change over time.

Discussion

This study represents an exceptional experience for a new drug, by virtue both of the characteristics of the study population and the duration of the exposure to vigabatrin.

The study had two main aims: (1) To assess the maintenance of efficacy on long-term therapy. (2) To investigate the long-term tolerability. This last point was of paramount importance in view of the animal toxicology data relating to dose and species-dependent intramyelinc oedema. All patients have thus been thoroughly monitored for CNS side effects, with repeated neurological examinations performed by a number of different investigators. All of them were aware of the animal toxicity findings.

With respect to the safety issue, long-term data proved very reassuring: there was a very low incidence (1.6%) of drop out for adverse events in those patients treated more than one year. Other adverse events were similar to those obtained in other studies: although adverse events must be weighted against the background of polytherapy in these patients, their incidence remained low, sedative adverse events being reported in 21.6% of patients and psychological events in 18.5%. Adverse events were mostly mild or moderate; moreover, they clearly moderated with continuation of therapy. These findings provide strong evidence against the development of any neurotoxicity in patients on long term therapy.

Long-term monitoring also demonstrated the maintenance of efficacy with continued vigabatrin therapy: only 11% of those patients treated for more than one year dropped out for insufficient efficacy, two thirds of them between 12 and 18 months. This indicates that once patients have been selected as responders the efficacy of vigabatrin is usually maintained. A certain rate of drop out on long term therapy is not unexpected in patients with severe epilepsy: large-scale multicentre studies of standard antiepileptic

drugs (such as that conducted in the Veterans Administration Cooperative study) show a drop-out rate of about 10% of patients between 12 to 24 months and rather lower numbers thereafter (Smith *et al.*, 1987). Finally, monitoring of seizure frequency in 2 and 3 year cohorts clearly shows the maintenance of seizure reduction over long periods of time with no sign of tachyphylaxis.

This study confirms and further extends previous reports that vigabatrin is an effective antiepileptic compound in severe drug-resistant epilepsies. In the long-term there is excellent tolerability and no evidence of tachyphylaxis.

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