Effects of long term vigabatrin on somatosensory evoked potentials in epileptic patients

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- 1 Vigabatrin has proved to be a very effective antiepileptic in clinical trials, with excellent long term tolerability.
- 2 The purpose of this study was to test the central nervous system (CNS) safety of the drug during long term clinical use, due to the existence of species-dependent intramyelinic oedema in animal toxicology studies.
- 3 Somatosensory evoked potentials were recorded repeatedly over a mean period of 11 months, in 54 adult patients with refractory epilepsy who received vigabatrin as add-on therapy to their current antiepileptic regime.
- 4 There was no suggestion throughout the study that vigabatrin could lead to a prolongation of neuronal conduction times within the CNS pathways.
- 5 The results are consistent with previous studies of somatosensory, visual and brainstem auditory evoked potentials in patients. In view of the results observed in the dog, where increases in central latencies of somatosensory evoked potentials were clearly apparent, these data provide strong reassurance about the neurological safety of vigabatrin in the treatment of epileptic patients.

Keywords vigabatrin somatosensory evoked potentials intramyelinic oedema animal toxicology

Introduction

Vigabatrin (γ -vinyl-GABA, GVG) has proved to be an effective anticonvulsant in refractory epilepsy (Hammond & Wilder, 1985a). However, during long term animal toxicology studies, vigabatrin has been shown to induce a non-progressive and reversible intramyelinic oedema in central white matter tracts (Butler *et al.*, 1987). No clinical sign of any neurotoxicity has been shown in humans, despite extensive monitoring in patients treated long term. However, particular attention has been paid to techniques capable of detecting clinically silent intramyelinic oedema: recording of evoked potentials is considered one of the most sensitive non-invasive methods of detecting subclinical

alterations of nerve conduction which are secondary to white matter lesions seen, for example, in multiple sclerosis (Chiappa, 1983). There is little doubt that this technique would detect subclinical intramyelinic oedema in vigabatrin treated patients. Indeed, in dogs receiving vigabatrin a marked increase in central latencies of somatosensory evoked potentials was shown to parallel the evolution of intramyelinic oedema, occurring after 5–7 weeks of exposure and returning to normal after drug withdrawal (Arezzo, 1987). The aim of the study was therefore to test the safety of vigabatrin in the central nervous system of epileptic patients as measured by somatosensory evoked potentials.

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Methods

Patients

Fifty-four patients suffering from drug resistant epilepsy and receiving vigabatrin as an add-on therapy in the course of clinical trial protocols participated in this study. Informed consent was given by each patient. There were 37 men and 17 women with a mean age of 29 years (range 14–65). Forty-five of these patients suffered from complex partial seizures with or without secondary generalization, seven from simple partial seizures, and two from primary generalized seizures.

Their current antiepileptic medication was unchanged during the study and consisted of one or more of the following drugs to which vigabatrin was added: carbamazepine, clobazam, clonazepam, phenacemide, phenobarbitone, phenytoin, primidone and valproate. The mean number of antiepileptic drugs (vigabatrin excluded) taken by each patient was 2.4.

Volunteers

Seven healthy volunteers also participated in this study. They consisted of six men and one woman, mean age 29 years (range 24–38) who were in good general health and were not taking any psychotropic or other medication.

Technical procedure

Where possible, the patients were investigated at the end of a placebo period prior to the beginning of vigabatrin treatment (baseline assessment) and following a period of treatment of at least 1 month. Stimulation of the median nerve at the wrist was performed with electrical square pulses of 100 μ s duration, delivered at a stimulus rate of 3.1 s⁻¹. The stimulus intensity was adjusted to obtain a muscular twitch of the abductor pollicis brevis muscle, at the threshold.

The electrodes were placed according to Erb's point ipsilateral, neck (CV3), scalp (FZ), scalp (C'3 or C'4), ear lobes (A1–A2). Recording parameters consisted of band pass 15–1500 Hz, with an analysis time of 50 ms. The number of trials to be averaged was 600.

Whenever possible, the following points were measured: N10, N14, P15, N20 and P25 on the somatosensory evoked potential curves. A digital filtering of the curves could be performed off-line. Central conduction times were derived from the calculation of N20–N10 and absolute values of N20.

Statistical evaluation

Recordings in patients who had no baseline assessment were withdrawn from the statistical analysis. A Student's *t*-test for paired data was used to compare the last assessment with baseline.

Results

In the 54 patients participating in this study, mean exposure to vigabatrin at the time of the last assessment was 11 months (range 1 to 25). As shown in Figure 1, mean values of N20 and N20–N10 showed no noticeable change over time for the following periods: before vigabatrin, after 0–3, 3–6, 6–12, 12–24 and over 24 months of treatment. The same figure also shows values recorded in healthy volunteers. When considered individually, none of the patients who had a baseline assessment showed a consistent increase in the central transmission times N20 and N20–N10 exceeding the acceptable limit of 12% (Figure 2).

Twenty patients who had had baseline recordings during the placebo run-in period and who had had at least one recording during vigabatrin treatment were considered in the statistical analysis. Shorter latencies were observed during vigabatrin periods as compared with baseline. The difference was small: a mean 3.3% decrease in N20 and a mean 3.4% decrease in N20–N10. However, the decrease was consistent, being observed in 15 out of 20 patients and statistically significant (paired *t*-test: $P < 0.001$ for both measurements). Other measurements showed no change, particularly in peripheral conduction times.

Figure 1 Mean N20 and N20–N10 values recorded during six successive periods of vigabatrin treatment. Numbers in bars indicate number of patients in each group. ▨ vigabatrin patients, □ healthy volunteers.

Figure 2 Individual evolution of the % change in N20-N10 values compared with baseline, in the 20 patients who had a baseline assessment.

Table 1 Central conduction times (mean $\pm$ s.e. mean) in healthy volunteers and in 20 patients before and during vigabatrin

	Healthy volunteers n = 7	Patients before vigabatrin n = 20	Patients after vigabatrin n = 20
N20	18.9 $\pm$ 0.2	20.1 $\pm$ 0.3	19.4 $\pm$ 0.3
N20-N10	9.0 $\pm$ 0.1	9.6 $\pm$ 0.2	9.3 $\pm$ 0.2

Table 1 shows the mean values of N20 and N20-N10 in healthy volunteers, and in these 20 patients at baseline and at the last recording during vigabatrin treatment. There was a significant difference between volunteer and patient measurements at baseline (two-tailed *t*-test, $P < 0.05$ for both values). However, this difference was no more significant when considering the last patient recordings during vigabatrin treatment.

Discussion

No increase in central latencies of somatosensory evoked potentials was observed on repeated assessments in 54 patients over a period of up to 25 months on vigabatrin.

The parameters chosen for measuring the central conduction were the latency of N20 and the difference between N20 and N10 latencies.

These parameters are likely to reflect the nervous conduction between brachial plexus at the level of the supraclavicular fossa and the primary somatosensory area (Desmedt & Cheron, 1980).

Interestingly, repeated measurements point to a tendency for central conduction times to decrease with time. Comparison of the last recording during vigabatrin treatment with the pre-treatment baseline indicates that this decrease, although small, is statistically significant. This could be due to an increase in conduction velocities, the mechanism of which would be unknown, or to a progressive sharpening of the N20 wave, which would lead to a better identification of its peak. Such a sharpening might be explained by a better signal extraction with an augmented signal to noise ratio. Whether this effect is due to an increased synchrony of the afferent volley to the cortex, relate to an increased GABAergic inhibition in sub-cortical relays, or to some change in the background EEG has yet to be proven.

The lack of increase in central latencies of somatosensory evoked potentials in vigabatrin-treated patients is in agreement with previous studies on somatosensory, visual and brainstem auditory evoked potentials (Cosi *et al.*, 1988; Hammond & Wilder, 1985b; Mervaala *et al.*, 1987). Because it is the length and amount of white matter tracts involved that determines the likelihood of detection of a myelin alteration, somatosensory evoked potential testing is pro-

bably the most accurate of the three modalities.

Our results must be interpreted in the light of data obtained in dogs, in whom a clear increase in central conduction times of somatosensory evoked potentials was shown to parallel the evolution of intramyelinic oedema (Arezzo, 1987). The absence of any change in humans is a strong argument in favour of the lack of vigabatrin neurotoxicity.

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