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A multicentre study of vigabatrin for drug-resistant epilepsy

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1 Vigabatrin (GVG) was given in a single-blind fashion to 89 patients with complex partial seizures (CPS) refractory to conventional drugs.

2 The median number of CPS per month decreased from 11.0 to 5.0 after addition of GVG, and 51% of patients had a 50% or greater decrease in CPS frequency ($P < 0.001$).

3 Side effects (principally drowsiness, ataxia, headache) occurred mainly during the initiation of therapy and decreased during therapy. After 12 weeks on GVG side effects significantly interfered with functioning in only 13% of patients, and the efficacy: toxicity ratio warranted continued administration in 74% of patients.

4 Co-administration of GVG resulted in a mean decrease of 20% in phenytoin serum concentration ($P < 0.001$).

5 Sixty-six patients having a favourable response to GVG during the single-blind study have been followed for 6–54 (median 33) months on GVG. Only 17 patients have dropped out of long-term follow-up due to break through seizures and/or side effects. No serious systemic or neurological toxicity has been detected.

Keywords vigabatrin complex partial seizures epilepsy

Introduction

In 1982 a multicentre study of vigabatrin (GVG) for refractory complex partial seizures (CPS) was initiated in the United States. Patients first participated in a single-blind trial of GVG. Patients having a favourable response to GVG during the single-blind trial entered into a long-term open-label follow-up study. The results of the single-blind study have been published in detail elsewhere (Browne *et al.*, 1987) and will be summarized in this paper. This paper will then report new results from the long-term follow-up phase of the study.

Methods

Patient selection

All patients met the following criteria: (1) CPS as defined by the International Classification of Epileptic Seizures (Dreifuss *et al.*, 1981); (2) 3 or more CPS per month; (3) taking no more than three of carbamazepine, phenytoin, phenobarbitone, or primidone at therapeutic serum concentration; (4) 18 years of age or older; (5) no hepatic, renal, or cardiac disease; (6) aetiology of seizures not treatable or progressive; (7) no evidence of alcohol or drug abuse; (8) no major

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depression or psychiatric disorder; (9) no intake of benzodiazepines or valproic acid within 2 weeks prior to entering study.

Study design

During the 'baseline phase' seizure calendars were kept for 12 weeks while patients continued taking their conventional antiepileptic drugs. During the last 4 weeks of the baseline phase ('placebo month') patients received GVG placebo in a single-blind fashion. GVG and placebo were administered orally as solutions with similar appearance and taste.

During the 'titration phase' patients were begun on GVG 1 g day^{-1}. The daily dose of GVG was increased by 1 g at weekly intervals until a dosage of 50 mg kg^{-1} day^{-1} or 4 g day^{-1}, whichever was less, was reached or toxicity precluded further increase.

During the 'maintenance phase' the final dose of GVG attained in the titration phase was administered for 12 weeks. The doses of conventional antiepileptic drugs remained unchanged throughout the baseline, titration and maintenance phases unless necessitated by suspected drug interactions with GVG. The single-blind was maintained throughout the titration and maintenance phases, and seizure calendars were kept.

After the single-blind study was completed, patients having a favourable response to GVG entered into an open-label long-term 'follow-up phase'. During the follow-up phase, GVG dosage could be adjusted for optimization, and concomitant medications could be removed.

Patients were seen at the following times: 4, 8, 10, and 12 weeks after entering the baseline phase; weekly during the titration phase; 2, 4, 8, and 12 weeks after entering the maintenance phase; every 3 months during the follow-up phase. At each visit a complete blood count, SMA 12, and urinalysis were performed. An electrocardiogram was performed during the baseline phase, at the end of the titration and maintenance phases, and every 6 months during the follow-up phase. Visual, auditory, and upper extremity somatosensory evoked potential tests were performed at the end of the maintenance phase in 75 patients. Visual evoked potentials were performed every 3 months on every patient during the follow-up phase.

Pharmacokinetic and analytic methods

At each visit a random sample for serum concentration of concomitant antiepileptic drugs was obtained. At one centre (Boston Veterans Administration Medical Center) all serum samples were collected in the fasting state at a fixed time after the last dose, and a portion of the fasting sample was frozen. At the end of the study the concentration of GVG was determined by the method of Smithers *et al.* (1985), and the total (and in some cases unbound) concentrations of concomitant antiepileptic drugs were determined by high performance liquid chromatography (Szabo & Browne, 1982) and free level system 1 (SYVA) ultrafiltration system for separation of free drug (Cronin *et al.*, 1981). All determinations for a given patient were performed on the same day. At one centre (Boston Veterans Administration Medical Center), the elimination half-life of GVG after chronic administration (15–47 weeks) was determined for five patients by measuring the GVG serum concentration by the method of Smithers *et al.* (1985) 4, 8, 12, 15, and 18 h after the last dose in patients having the drug stopped for lack of efficacy and/or toxicity.

Statistical methods

The mean and median monthly seizure frequencies for each 4-week study 'month' were calculated for each patient and for all patients combined. The Kolmogorov-Smirnov test (K-S test) (Beyer, 1968) was performed comparing distribution of CPS frequencies for each patient during the 3 baseline months with the 3 maintenance months. For each subject the percent change in mean monthly seizure frequency between baseline and maintenance phases was tested against a theoretical expected change of 0% by the Student's test (Beyer, 1968). The mean monthly seizure frequency during the baseline period for each patient was also compared with his mean monthly seizure frequency during the maintenance phase by the Wilcoxon matched-pairs signed rank test (Beyer, 1968).

Results

Efficacy during single-blind phase

Eighty-nine patients entered the study, and 84 completed the single-blind phase. Two patients (2%) were dropped before the end of the maintenance phase because of presumed GVG toxicity. Three patients (3%) were dropped before the end of the maintenance phase due to increased seizure frequency or duration. The median number of CPS per month for the 84 patients completing the maintenance phase was 11.0 during each of the first 2 baseline months,

10.5 during the placebo month, 6.0 during the titration month, and 5.0 during each of the 3 maintenance phase months. The distributions of CPS frequencies were significantly equivalent by the K-S test during the 3 baseline months ($\chi^2 = 1.89$, $P < 0.95$) and during the 3 maintenance months ($\chi^2 = 2.73$, $P < 0.99$). The distributions of CPS frequencies during the 3 baseline months were significantly different from the distributions during the 3 maintenance phase months by K-S test ($\chi^2 = 29.85$, $P < 0.001$).

Over the entire 12 week maintenance phase, 7% of patients had complete control of CPS, and 51% of patients had a 50% or greater reduction in CPS frequency (Table 1). During the last 4 weeks of the maintenance phase, 15% of patients had complete control of CPS, and 55% of patients had a 50% or greater reduction in CPS frequency. The differences in patients' CPS frequency between the 3 baseline months and the 3 maintenance months were significant ($P < 0.001$) by the Wilcoxon matched-pairs signed rank test. The mean shift of seizure frequency for all patients was a 48.3% decrease, which was significant when compared with a theoretical expected shift of 0% ($t = 12.44$, $P < 0.001$).

At the end of the maintenance phase a global evaluation of the efficacy to toxicity ratio for each of the 89 patients was performed. In 74% of patients the efficacy to toxicity ratio warranted continued administration of GVG. Fifty-five percent of patients had a 50% or greater reduction in CPS. Nineteen percent of patients had a reduction in the duration and/or severity of CPS which was sufficient to justify continued administration of the drug. GVG was discontinued due to lack of efficacy and/or toxicity in 26% of patients.

Toxicity during single-blind phase

The most frequently reported adverse events were drowsiness, ataxia, headache, irritability, dizziness, and unsteadiness (Table 2). The incidence and severity of these side effects were greatest during the titration phase and progressively decreased during the maintenance phase. At the end of the maintenance phase only drowsiness was present in more than 10% of patients.

At the end of the maintenance phase the physicians' global evaluation of adverse events on GVG was as follows: no adverse events, 47% of patients; adverse events present but do not significantly interfere with patient functioning, 40% of patients; adverse events significantly interfere with patient functioning, 13% of patients.

Clinical pharmacology and drug interactions during single-blind study

GVG dosage, serum concentration, and elimination half-life data are shown in Table 3. GVG serum concentration ($\mu g\ ml^{-1}$) correlated significantly with GVG dosage ($mg\ kg^{-1}\ day^{-1}$) ($r = 0.857$; $P < 0.01$). GVG serum concentration did not correlate significantly with reduction in CPS frequency (% decrease) ($r = -0.068$). Statistically significant ($P < 0.05$) decreases in the serum concentrations of phenytoin (−20%), phenobarbitone (−7%), and primidone (−11%) occurred during GVG co-administration when evaluated for the entire group. Similar changes in serum concentration were obtained in the substudy in which fasting levels were determined and between day and between centre analytic variability were eliminated (Browne *et al.*, 1987).

Table 1 Changes in CPS frequency during maintenance phase of single-blind study

Change in CPS frequency when compared with baseline phase	*12 week maintenance phase (% of patients)*[a]	*Last 4 weeks of maintenance phase (% of patients)*[a]
100% decrease	7%	15%
75%–99% decrease	19%	18%
50%–74% decrease	25%	22%
1%–49% decrease	34%	27%
No change or increase Less than 20%	10%	12%
Dropped before end of study due to toxicity	2%	2%
Dropped before end of study due to increased seizure frequency or duration	3%	3%
Total	100%	100%

[a] $n = 89$

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Table 2 Most frequently reported adverse events due to GVG during single-blind study[a]

Adverse event	*Titration phase (% patients)*[b]	*Maintenance phase*		
		Month 1 (% patients)[c]	*Month 2 (% patients)*[d]	*Month 3 (% patients)*[e]
Drowsiness	40	34	26	20
Ataxia	11	9	6	7
Headache	10	9	6	6
Irritability	8	8	9	8
Dizziness	8	6	1	2
Unsteadiness	6	2	2	2
Any side effect	71	61	54	45

[a] See text for description of adverse events during follow-up phase
[b] $n = 89$, [c] $n = 87$, [d] $n = 85$, [e] $n = 84$
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Table 3 Clinical pharmacology of GVG

	Range	*Median*
Maintenance phase GVG dose (g day^{-1}, $n = 88$)	1–4	3.2
Maintenance phase GVG dose (mg kg^{-1} day^{-1}, $n = 88$)	10.2–63.0	45.1
Steady state fasting GVG serum concentration ($\mu g\ ml^{-1}$,[a] $n = 10$)	0.7–13.4	4.0
Ratio of GVG serum concentration/GVG dose ($\mu g\ ml^{-1}$:mg kg^{-1} day^{-1}, $n = 10$)	0.080–0.298	0.143
GVG elimination half-life (h, $n = 5$)	4.2–5.6	5.3

[a] Conversion factor for GVG serum concentration units: 1 $\mu g\ ml^{-1} = 7.7\ \mu M$
From Browne *et al.* (1987) with permission.

Follow-up phase

Sixty-six patients entered this phase and have been followed for 6 to 54 (median 33) months. Durations of therapy include the 4 months on GVG during the single-blind phases of the study. GVG dosage was increased in eight patients, decreased in five patients, and both increased and decreased in four patients during the follow-up phase. One or more concomitant medications were removed in 14 patients during the follow-up phase.

Thirty-one patients continue to take GVG and have been followed for 44 to 54 (median 49) months. Thirty-five patients discontinued GVG during the follow-up phase after taking GVG for 6 to 49 (median 19) months. The reasons for discontinuing GVG were: benefit-to-risk evaluation—8, seizure break through—6, adverse events—6, seizure break through and adverse events—5, moved or lost—4, no longer eligible for study—2, death—2, elicit drug abuse—1, patient request—1. Benefit-to-risk evaluation drop outs were persons who had only a modest decrease in seizure frequency on GVG and were dropped because emerging animal toxicity findings dictated dropping persons not having considerable improvement on GVG. The two deaths were unrelated to GVG treatment (myocardial infarction and motor vehicle accident). One patient requested to leave the study despite having a 95% decrease in CPS frequency, because he was dissatisfied at having less than complete control. The times of drop out appeared to be random throughout the period of follow-up.

The most common side effects reported during the follow-up phase were: drowsiness, ataxia, headache, dizziness, diplopia, memory disturbance, rash, and speech disturbance. No clinically important abnormalities were detected during any phase of this study on any of the laboratory studies, including evoked responses (Smith *et al.*, 1985).

Forty-one of the 66 patients entering the follow-up phase had a 50% or greater decrease in CPS frequency in comparison with their baseline value. The other 25 patients had had an important decrease in the duration or severity of their CPS. At every 6 months follow-up evaluation to date (up to 54 months) over 60% of

patients remaining on GVG have had a 50% or greater reduction in CPS frequency in comparison with baseline CPS frequency (Table 4). Twenty-two of the cohort of 41 patients having a 50% or greater decrease in CPS frequency in comparison with the baseline phase during the single-blind study remain in the follow-up study, and the majority have retained their 50% or greater decrease in CPS frequency during each time interval of the period of long-term follow-up.

Discussion

Short-term efficacy

The efficacy of GVG in reducing CPS frequency in our study corroborates the predictions of animal studies and the findings of other clinical studies presented in this volume. The efficacy of GVG in clinical studies provides strong support for the views that GABA is important in controlling seizures and that development of GABA agonists is a productive approach for development of antiepileptic drugs. The results of our study need to be confirmed with large double-blind studies to exclude placebo effect and/or observer bias. Small double-blind studies of GVG for refractory CPS report results similar to ours (Gram *et al.*, 1985; Loiseau *et al.*, 1986; Rimmer & Richens, 1984; Tassinari *et al.*, 1985; Tartara *et al.*, 1986), and large double-blind studies are now in progress (Mumford & Dam, 1989).

Short-term toxicity

The short-term incidence and severity of side effects in our study were similar to those reported in other trials (Gram *et al.*, 1985; Loiseau *et al.*, 1986; Pederson *et al.*, 1985; Rimmer & Richens, 1984; Schechter *et al.*, 1984; Tassinari *et al.*, 1987; Tartara *et al.*, 1986). Clinical trails to date indicate GVG has a favourable short-term efficacy: toxicity ratio in the majority of patients.

Clinical pharmacology

The short elimination half-life of GVG does not imply a short duration of action. The duration of action of GVG is probably much longer than its serum elimination half-life, because GVG irreversibly binds to brain GABA transaminase. In single dose studies with GVG in mice, maximal inhibition of whole brain GABA transaminase persisted for 48 h, and a 40% inhibition of whole brain GABA transaminase activity was found after 6 days (Merrell Dow Research Institute, unpublished data). Our clinical experience was that the full clinical and toxicological effects of increasing or decreasing GVG dosage did not become apparent until 2 to 10 days after the change.

Drug interactions

The mechanism of our observed decreases in serum concentration of phenytoin, phenobarbitone, and primidone is unknown. Alteration in protein binding was excluded as a cause (Browne *et al.*, 1987).

The decreases in phenytoin serum concentration after adding GVG were associated with increased seizure frequency and a need for increased dosage in some patients. The absolute changes in serum concentrations of phenobarbitone and primidone were small, did not appear to alter seizure control, and did not necessitate dosage changes.

Table 4 Changes in CPS frequency during long-term phase

Duration of GVG therapy[a] *(months)*	*Number of patients*	*Patients with > 50% reduction (%)*[b]
10	59	61
16	46	69.5
22	41	63.4
28	36	61.1
34	28	64.3
40	29	68.9
46	28	75
52	12	66

[a] The duration includes the 4 months of the single-blind study
[b] > 50% reduction in CPS frequency when compared with baseline phase frequency

Long-term efficacy

Perhaps the most encouraging aspect of our study was the low incidence of break-through seizures (11 of 66 patients) during a median of 33 months of follow-up. The long-term (mean 9.3 months of follow-up) study of Pedersen *et al.* (1985) reported no break-through seizures. In trials of additive drugs for refractory CPS, it is not uncommon for patients to have a significant reduction in CPS for several months and then to relapse to their former seizure frequency (e.g., Browne *et al.*, 1983). The combination of high initial response rate and low rate of break-through seizures in long-term follow-up make GVG a particularly promising therapy for refractory CPS.

Long-term toxicity

The results of this and other studies (Liegeois-Chauvel *et al.*, 1989; Pedersen *et al.*, 1985; Smith *et al.*, 1985) indicate no serious systemic or neurological toxicity associated with chronic GVG administration.

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