Epilepsia, **40**(Suppl. 6):S13–S16, 1999
Lippincott Williams & Wilkins, Philadelphia

Monotherapy Trials with Gabapentin for Partial Epilepsy

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Summary: The efficacy and safety of gabapentin as monotherapy for treatment of partial onset seizures were evaluated in three large multicenter, double-blind, parallel-group, dose-controlled trials. In the first trial, 275 outpatients with refractory partial epilepsy maintained on stable doses of one or two antiepileptic drugs (AEDs) were switched to gabapentin (GBP) monotherapy at 600 mg, 1200 mg, or 2400 mg daily. Patients were required to exit the 26-week double-blind phase of the study if they experienced worsening of seizure frequency. With respect to time to exit, there was no statistically significant difference among the three groups; only 3% of patients withdrew from the trial because of adverse events. In the second study, 82 hospitalized patients with medically refractory epilepsy were tapered off baseline AEDs and randomly assigned to GBP monotherapy at 300 mg/day or 3600 mg/day. Patients remained in the trial for a maximum of 8 days but had to exit the trial if they experienced one or more exit events. Time to exit was significantly longer in patients in the 3600-mg group (151 h) compared with those in the 300-mg group (85 h) ($p = 0.0001$). None of the patients withdrew from the trial because of side effects. In the third study, 292 patients with newly diagnosed partial seizures were randomized to GBP 300, 900, or 1800 mg/day or to carbamazepine (CBZ) 600 mg/day. Patients remained in the trial for up to 6 months or until they experienced an exit event. Mean time to exit was significantly longer for patients who received GBP 900 mg/day ($p = 0.02$) or 1800 mg/day ($p = 0.04$) compared with those who received 300 mg/day. The completion rate for the CBZ group (37%) was similar to that of the GBP 900-mg (39%) and 1800-mg (38%) groups. Patients receiving CBZ had a higher withdrawal rate because of adverse events compared with the GBP 900-mg and 1800-mg groups. The results of these trials provide good evidence of the efficacy and safety of GBP as monotherapy for the treatment of partial-onset seizures. **Key words:** Gabapentin—Monotherapy—Newly diagnosed seizures—Partial-onset seizures—Refractory epilepsy.

Gabapentin (GBP) is approved as adjunctive therapy for the treatment of partial-onset seizures in patients at least 12 years of age, based on the results of three large, multicenter, double-blind, placebo-controlled, dose-ranging, parallel-group clinical trials (1–3). In all three studies, patients randomized to GBP at daily doses between 600 and 1800 mg had a statistically significant reduction in seizures compared with placebo-treated patients. More recently, the safety and efficacy of GBP as monotherapy were evaluated in three clinical trials in adult patients with refractory and newly diagnosed partial epilepsy as well as in children with newly diagnosed partial epilepsy of childhood with centrotemporal sharp waves (rolandic epilepsy). The pediatric trial is reviewed elsewhere in this supplement.

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OUTPATIENT CLINICAL TRIAL IN PATIENTS WITH REFRACTORY PARTIAL EPILEPSY

This was a multicenter, randomized, double-blind, dose-response clinical trial performed on patients with refractory partial epilepsy (4). The study consisted of an 8-week baseline phase followed by a 26-week double-blind phase. Eligible patients were 12 years or older, with at least four complex partial or secondarily generalized seizures during the baseline phase while maintained on stable doses of one or two antiepileptic drugs (AEDs). After the baseline phase, qualifying patients were randomized to receive GBP at daily doses of 600 mg, 1200 mg, or 2400 mg taken on a tid schedule. To maintain their safety, patients were required to exit the study if they experienced protocol-defined worsening of seizure frequency during the double-blind phase. A total of 275 patients were randomized in this trial, with no statistically significant difference in time to exit, the primary efficacy variable, among the three dosage groups. GBP was very well tolerated in this trial, with only 3% of patients exiting because of adverse events. The most

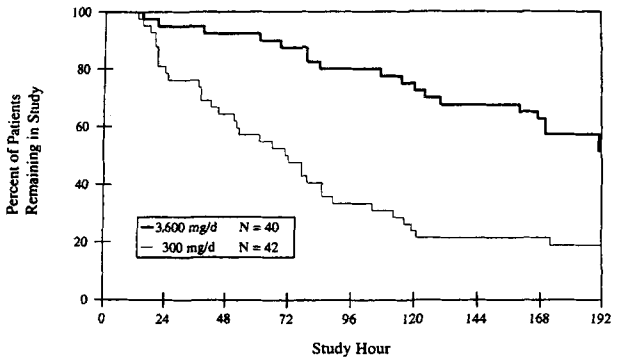

FIG. 1. Kaplan–Meier estimate of time to exit. Patients in the 3600-mg/d gabapentin dosage group remained in the study significantly longer than the patients in the 300-mg/d gabapentin group ($p = 0.0001$, generalized Wilcoxon's test). From Bergey et al. (7).

common adverse events, dizziness and somnolence, were transient in the majority of patients.

The results of this trial were uninformative (5) because of the lack of a significant dose–response relationship. This may have been due to the trial design, the refractory nature of the patient population studied, the occurrence of withdrawal seizures, and the limited range of GBP dosages compared. Results from the open-label phase of this trial that allowed titration of GBP up to 4800 mg/day suggested that higher GBP dosages are effective as monotherapy in a subgroup of patients with refractory partial epilepsy (6).

INPATIENT CLINICAL TRIAL IN HOSPITALIZED PATIENTS WITH REFRACTORY PARTIAL EPILEPSY

In this double-blind trial, patients at least 12 years of age with refractory partial epilepsy admitted for CCTV–EEG monitoring as part of their presurgical work-up for epilepsy were randomized to GBP monotherapy at 300 mg/day or 3600 mg/day (7). The full dose of GBP was administered on day 1 in three equally divided doses

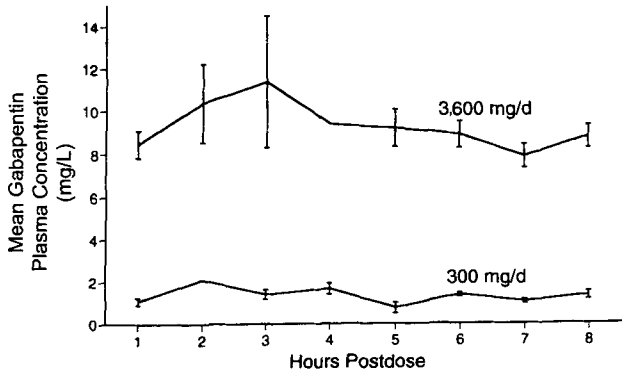

FIG. 2. Mean gabapentin plasma concentrations at trough were about sevenfold higher for the 3600-mg/d dosage group than for the 300-mg/d dosage group. From Bergey et al. (7).

every 8 h. Patients remained in the trial for a maximum of 8 days but had to exit the trial if they experienced a total of four complex partial or secondarily generalized seizures, a single generalized tonic–clonic seizure if none was previously experienced, status epilepticus, or a clinically significant intensification in seizure duration or severity. A total of 82 patients were randomized in this trial, with time to exit, the primary efficacy variable, being significantly longer in patients randomized to the high dosage group (mean time 151 h) compared with the low dosage group (mean time 85 h) ($p = 0.0001$) (Fig. 1). The results of the secondary efficacy variable, percentage of patients who completed the trial, were consistent with the primary outcome data. A total of 53% of patients in the 3600-mg/day group completed the trial compared with 17% of those in the 300-mg/day group ($p = 0.002$). Trough GBP serum levels averaged 9 mg/L in the 3600-mg/day group and 1 mg/L in the 300-mg/day group (Fig. 2). Despite rapid administration of full-dose GBP at 3600 mg/day, none of the patients exited the trial because of side effects. The most common adverse events in the 3600-mg/day group were dizziness, ataxia, and somnolence (Table 1).

This trial demonstrated the short-term anticonvulsant properties of GBP as monotherapy and showed that this drug can be safely initiated at 3600 mg/day if needed, at least in an inpatient setting.

OUTPATIENT CLINICAL TRIAL IN PATIENTS WITH NEWLY DIAGNOSED PARTIAL SEIZURES

This was a multicenter, double-blind, dose-controlled clinical trial designed to evaluate the safety and efficacy of GBP as monotherapy for patients with newly diagnosed partial epilepsy (8). Eligible patients were 12 years or older with a history of at least two unprovoked partial seizures, with or without secondary generalization, in the

TABLE 1. *Most commonly occurring adverse events [no. (%) of patients]*[a]

	Gabapentin dosage	
Adverse event	300 mg/d ($n = 42$)	3600 mg/d ($n = 40$)
Dizziness	4 (9.5)	7 (17.5)
Ataxia	2 (4.8)	8 (20.0)
Somnolence	3 (7.1)	6 (15.0)
Paresthesia	4 (9.5)	4 (10.0)
Nystagmus	2 (4.8)	5 (12.5)
Fatigue	3 (7.1)	4 (10.0)
Headache	3 (7.1)	3 (7.5)
Dysarthria	0 (0.0)	5 (12.5)
Myalgia	1 (2.4)	3 (7.5)
Anorexia	2 (4.8)	2 (5.0)
Tremor	1 (2.4)	3 (7.5)

[a] Adverse events experienced by more than three patients. Adapted from Bergey et al. (7).

TABLE 2. *Completion, exit, and adverse event withdrawal rates*[a]

	Gabapentin (mg/d)			Carbamazepine (600 mg/d)
	300 (n = 72)	900 (n = 72)	1800 (n = 74)	(n = 74)
Completion rate	18 (25.0)	28 (38.9)	28 (37.8)	27 (36.5)
Exit rate	45 (62.5)	29 (40.3)	32 (43.2)	22 (29.7)
AE withdrawal rate	0 (0.0)	3 (4.2)	10 (13.5)	18 (24.3)
Exit + AE withdrawal rate	45 (62.5)	32 (44.4)	42 (56.8)	40 (54.1)

AE, adverse event.
[a] Values are number (%) of patients.
From Chadwick et al. (8).

previous 6 months. Qualifying patients were randomized in a double-blind fashion to GBP at 300 mg/day, 900 mg/day, or 1800 mg/day. There was also a comparative group who received CBZ at 600 mg/day in an open-label fashion. Patients remained in the trial for up to 6 months but had to exit if they experienced a single secondarily generalized seizure or three partial seizures. A total of 292 patients were randomized in this trial, with 72–74 patients in each treatment group. Time to exit was significantly longer for patients who received GBP 900 mg/day or 1800 mg/day compared with those who received 300 mg/day (p = 0.02 and 0.04, respectively). Although the CBZ group could not be included in the statistical analysis, the completion rate for patients in that group (37%) was similar to that of the GBP 900-mg (39%) and 1800-mg (38%) groups (Table 2). Overall, patients who received CBZ had a lower exit rate but a higher rate of withdrawal due to adverse events, compared with the GBP 900-mg and 1800-mg groups (Table 2). The most common adverse events experienced by GBP-treated patients were dizziness, headache, and fatigue (Table 3).

In this trial, a significant dose–response relationship was demonstrated, providing evidence for the efficacy of GBP monotherapy in patients with newly diagnosed partial epilepsy. It also suggested that an appropriate starting dose in this patient population is 900 mg/day. As with other AEDs, the dose should be gradually titrated to efficacy or tolerability in case of seizure recurrence.

CONCLUSIONS

On the basis of the results of the aforementioned trials, there is now growing evidence to support the efficacy of GBP as monotherapy for the treatment of partial-onset seizures. The exit task is to define specific patient populations with partial epilepsy in whom the pharmacokinetic and/or safety profile of GBP would make it an attractive choice as monotherapy. Some of those populations include patients with porphyria, hepatic disease, elderly patients receiving polytherapy, children with benign partial epilepsies of childhood, and patients receiving immunosuppressants. For example, there is now evidence, derived from cell cultures and clinical reports, that GBP does not increase porphyrin production in patients with porphyrias, making it a first-line agent for the treatment of seizures in these disorders. In addition, GBP is the only AED, except for vigabatrin, that is not hepatically metabolized, and it would therefore be very useful as monotherapy for patients with seizures and liver disease. Seizures in the elderly are usually easily controlled, but patients in this age group are much more sensitive to the adverse events of AEDs. Elderly patients

TABLE 3. *Adverse events occurring in at least five gabapentin-treated patients*

	Gabapentin (mg/d)			Carbamazepine (600 mg/d)
Adverse event	300 (n = 72)	900 (n = 72)	1800 (n = 74)	(n = 74)
Dizziness	5	11	11	10
Headache	10	10	10	10
Fatigue	9	9	6	22
Nausea or vomiting	4	5	6	9
Somnolence	2	5	5	10
Viral infection	1	5	4	4
Abdominal pain	3	3	4	1
Nervousness	1	3	5	0
Weight increase	4	2	2	1
Increased appetite	0	4	4	2
Rhinitis	2	4	1	3
Bronchitis	2	2	2	0
Paresthesia	2	2	1	1
Pharyngitis	1	1	3	2

From Chadwick et al. (8).

also tend to be receiving a number of prescription medications, many of which are metabolized in the liver (9–11) and can lead to significant drug–drug interactions in the presence of AEDs that have a propensity to induce or inhibit hepatic microsomal enzymes. The safety of GBP and its lack of drug–drug interactions make it a very attractive choice in this patient population. Its lack of drug–drug interaction is also an advantage in patients with partial seizures who are receiving concurrent treatment with immunosuppressive drugs.

What is now needed are comparative randomized clinical trials between GBP and the standard AEDs for patients with newly diagnosed partial epilepsy, to evaluate the relative safety and efficacy of this AED. In addition, clinical trials in specific patient populations with partial epilepsy would be very helpful in better defining the role of this AED as monotherapy.

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