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Lamotrigine versus Valproic Acid as First-line Monotherapy in Newly Diagnosed Typical Absence Seizures: An Open-label, Randomized, Parallel-group Study

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Summary: *Purpose:* To compare the efficacy of lamotrigine (LTG) and valproic acid (VPA) in newly diagnosed children and adolescents with typical absence seizures.

Methods: A randomized**,** open-label parallel-group design was used. After undergoing an awake video-EEG recording, which included one to two trials of 3 min of hyperventilation and intermittent photic stimulation, eligible patients were randomized to receive LTG or VPA. LTG was initiated at a daily dose of 0.5 mg/kg for 2 weeks in two divided doses, followed by 1.0 mg/kg/day for an additional 2 weeks. Thereafter, doses were increased in 1-mg/kg/day increments every 5 days until seizures were controlled, intolerable adverse effects occurred, or a maximum dose of 12 mg/kg/day had been reached. VPA was equally uptitrated according to clinical response, starting at 10 mg/kg and increasing by 5 mg/kg/24 h every 3 days, if required, to a maximum of 30 mg/kg/day in three divided doses. Patients were seen in the clinic every month for $\leq$12 months.The primary efficacy end point at each visit was seizure freedom, defined as lack of clinically observed seizures since the previous visit and lack of electroclinical seizures during ambulatory 24-h EEG testing and a video-EEG session with hyperventilation.

Results: Thirty-eight children (17 boys, 21 girls), aged from 3 to 13 years (mean, 7.5 years), all newly diagnosed with childhood or juvenile typical absence seizures, were enrolled. After 1 month of treatment, 10 (52.6%) of 19 children taking VPA and one (5.3%) of 19 taking LTG were seizure free ($p = 0.004$). By the 3-month follow-up, 12 (63.1%) children taking VPA and seven (36.8%) taking LTG were controlled ($p = 0.19$). After 12 months, 13 children taking VPA (dose range, 20–30 mg/kg/day; mean serum level, 76.8 mg/L; range, 51.4–91 mg/L) and 10 taking LTG (dose range, 2–11 mg/kg/day; mean serum level, 8.1 mg/L; range, 1.1–18 mg/L) were seizure free ($p = 0.51$). Side effects were mostly mild and transient and were recorded in two (10.6%) children treated with VPA and in six (31.8%) treated with LTG.

Conclusions: Both VPA and LTG can be efficacious against absence seizures, although VPA shows a much faster onset of action, at least in part because of its shorter titration schedule.
Key Words: Lamotrigine—Valproic acid—Typical absences—Monotherapy.

Valproic acid (VPA) and ethosuximide (ESM) have been shown to be equally effective as monotherapy for typical absence seizures (1,2), and, at present, they are generally considered first-choice drugs for this seizure type. VPA controls absences in ~75% of patients, in addition to being effective against generalized tonic–clonic seizures (70%) and myoclonic seizures (75%). However, its use may involve safety risks for postmenarchal women (3).

ESM produces complete control of absences in 70% of treated patients (4,5), but it is unsuitable as monotherapy when other generalized seizure types coexist. Recently, lamotrigine (LTG) was shown to be effective as both add-on and monotherapy for typical absence seizures and generalized tonic–clonic seizures in ~50 to 60% of patients (6–12), although it may worsen myoclonic jerks (13), and skin rashes are a concern (14). Although it has been suggested that LTG may be used as an alternative to VPA and ESM in the management of epilepsies associated with absences (15), prospective randomized comparative trials of the efficacy of VPA and LTG in typical absence seizures are not available. One additional concern is that the slow titration schedule of LTG may result in a longer latency to achieve seizure control in de novo–treated patients.

This open-label, randomized, parallel-group study was designed to compare the efficacy of LTG and VPA as

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first-line drugs in the treatment of children and adolescents newly diagnosed with typical absence seizures.

MATERIALS AND METHODS

Subjects

Patients were selected based on the following inclusion criteria: (a) age from 3 to 13 years; (b) newly diagnosed typical absence seizures (International League Against Epilepsy; ILAE Commission, 1981) (16) associated with generalized, synchronous 3-Hz (2.5–4 Hz) spike-and-wave activity, lasting >3 s, occurring spontaneously or during one of two trials of 3-min hyperventilation with a 1- to 2-min rest between trials; (c) clearly observable clinical signs of typical absence seizures (e.g., staring or impairment of consciousness) on the video record; (d) normal clinical, neurologic, and computed tomography (CT)/magnetic resonance imaging (MRI) examination; and (e) informed consent by parents or caregivers. Exclusion criteria were (a) absences with marked eyelid or perioral myoclonus (eyelid or perioral myoclonia with absences); (b) absences with marked limb and trunk rhythmic myoclonic jerks (myoclonic absence epilepsy); (3) absences with single ictal myoclonic jerks of the limbs, trunk, or head; (d) absences with mild or not clinically detectable impairment of consciousness (e.g., juvenile myoclonic epilepsy); (e) other types of epileptic seizures; (f) stimulus-sensitive absences: photosensitive, pattern-sensitive, self-induced pattern-sensitive; (g) irregular, arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency; (h) central-temporal or occipital focal EEG discharges or abnormal background EEG activity; (i) known or suspected structural brain lesion; (j) progressive neurologic illness; (k) psychiatric disorder requiring medication; (l) chronic cardiovascular, renal, or hepatic disease and, in general, any disease that could interfere with drug absorption, distribution, metabolism, or excretion; (m) long-term comedication with other drugs; and (n) suspected poor compliance.

The protocol was approved by the local Ethics Committee, and the study was not sponsored by any commercial organization.

Study design

The study used an open-label, randomized, parallel-group design. After obtaining informed consent, each child or adolescent referred with a clinical presentation consistent with typical absences underwent an awake video-EEG recording that included one to two trials of 3 min of hyperventilation (HV-EEG) and intermittent photic stimulation (IPS). All EEG recordings were obtained by using a bipolar longitudinal and median transverse chain electrode configuration together with synchronous electromyographic recording from both deltoids, by using a Micromed recorder system. If the recording confirmed the presence of typical absence seizures, the patients were randomized to receive LTG or VPA. To prevent bias that may occur when the treating physician has access to the randomization code, the randomization list was controlled by an external investigator.

LTG was initiated, as in the study by Frank et al. (9), at a daily dose of 0.5 mg/kg for 2 weeks in two divided doses, followed by 1.0 mg/kg/day for an additional 2 weeks. Thereafter, doses were increased in 1-mg/kg/day increments every 5 days until seizures were controlled (as indicated by lack of clinical evidence of absences and no electroclinical seizures in an awake video-EEG with HV-EEG and in a 24-h ambulatory EEG), intolerable adverse effects occurred, or a maximum dose of 12 mg/kg/day had been reached. The ceiling dosage was based on the data by Frank et al. (9), suggesting that little additional benefit is obtained at doses >10 to 12 mg/kg/day. According to this titration schedule, the maximum allowed dose of LTG in patients completing without interruption the full uptitration schedule was reached ~75 days after initiation of treatment.

VPA (administered as 200-mg enteric-coated non–sustained-release sodium valproate tablets or, in some cases, as liquid formulation, 40 mg/ml) was started at 10 mg/kg/day and increased by 5 mg/kg/day every 3 days until seizures were controlled or intolerable side effects occurred, up to a maximum of 30 mg/kg/day given in three divided doses. These doses reflect the usual effective VPA dosage range (17). Dosages >30 mg/kg/day, which require special monitoring of clinical chemistry and hematologic parameters (18), were not tried.

Each patient was seen in the clinic at monthly intervals for ≤12 months and exited the study if they were not satisfactorily controlled at the highest dosage tested. At each visit, the evaluation included questioning of patients and parents/caregivers about clinical absences and side effects (recorded in a diary), a medical examination, and a video-EEG recording that included HV-IPS. If the video-EEG did not show evidence of absences, a 24-h ambulatory EEG monitoring also was performed. Laboratory evaluations at each visit included serum VPA and LTG levels (measured before the first daily dose, only after titration had been completed), a full blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), urea, creatinine, and urinalysis. Visits could be brought forward if telephone contacts provided information suggestive of uncontrolled absences.

Outcome assessment

Patients were considered "seizure free" when, at any visit, no clinical absences had been reported by external observers for at least the previous month, and no electroclinical seizures were detected in an awake video-EEG with HV-EEG and in a 24-h ambulatory EEG monitoring.

All video-EEG recordings and 24-h ambulatory EEGs were examined by two independent expert electroencephalographers, unaware as to which treatment a given patient had been randomized.

The primary efficacy measure was prospectively defined as the proportion of patients who remained seizure free during the treatment phase in each group. As at the time the protocol was designed, no sufficient information was available to formulate hypotheses on the comparative efficacy of the two drugs, the study was conceived as an exploratory trial, and the exploratory sample size was set at 38 without formal power calculations. The χ^2 test was used to test differences in proportions between treatment groups. All randomized patients were included in the analysis.

RESULTS

All patients were enrolled at the Epilepsy Unit of the Clinic of Child Neuropsychiatry and included 17 boys and 21 girls, ranging in age from 3 to 13 years (mean, 7.5 years), and all had newly diagnosed childhood or juvenile typical absence seizures. Mean duration of epilepsy was 6 months (range, 1–17 months); a family history for epilepsy was found in 17 (44.7%) patients and a history of febrile seizures in six (15.8%). Neurologic and neuroradiologic (CT/MRI) findings as well as cognitive levels were normal in all patients. Clinical characteristics (mean age, sex**,** family history of epilepsy and/or febrile convulsions, neurologic examination, mean duration of epilepsy) were comparable in both study groups, although a trend was noted for overrepresentation of girls and a shorter duration of epilepsy in the LTG group (Table 1).

Outcome findings are summarized in Table 1. Overall, nine patients (three in the VPA group and six in the LTG group) exited the study before completion of the 12-month follow-up. All discontinuations were due to lack of efficacy and occurred after 3 months in both groups. Some children, who were considered improved, continued on the assigned treatment throughout the study, although not all the criteria required for a definition of seizure freedom were met.

After 1-month treatment, 10 (52.6%) patients taking VPA and one (5.3%) patient taking LTG were seizure free ($p = 0.004$). At 3 months, seizure freedom was observed in 12 (63.1%) patients taking VPA (mean dosage, 22.6; range, 20–25 mg/kg; mean serum concentration, 73.5; range, 56–86 mg/L) and in seven (36.8%) patients taking LTG (mean dosage, 6.5; range, 2–11.5 mg/kg; mean serum concentration, 7.3; range, 1.3–15 mg/L), the difference failing to reach statistical significance ($p = 0.19$). At the last observation after 12-month follow-up, 13 (68.4%) patients taking VPA and 10 (52.6%) taking LTG were seizure free ($p = 0.51$). Among the patients seizure free at the last visit, mean duration of seizure freedom was 10.5 months (range, 8–11 months) in the VPA group and 8.9 months (range, 8–11 months) in the LTG group. Mean dosages at the last follow-up were 25.4 mg/kg (range, 20–30 mg/kg) for VPA and 8.3 mg/kg (range, 2–12 mg/kg) for LTG. These were associated with serum concentrations of 76.8 (range, 51–91) and 8.1 (range, 1.1–18) mg/L, respectively**.**

Adverse effects were recorded in two (10.6%) of the patients randomized to VPA (diarrhea, one; weight gain, one) and in six (31.8%) of those randomized to LTG (headache, two; transient mild skin rash after 1 week of treatment, one;

TABLE 1. *Characteristics of patients and outcome data*

	VPA group (n = 19)	LTG group (n = 19)
Sex (n)	M,10; F, 9	M, 7; F, 12
Familiarity for epilepsy (n)	7	10
Familiarity for febrile seizures (n)	4	2
Normal neurologic examination and IQ (no.)	19	19
Mean duration of epilepsy (mo)	6.9	4.5
Mean age at seizure onset (yr)	7.5 (range, 3–13)	7.5 (range, 4–12)
Daily dose (mg/kg, mean and range) at		
3 mo	22.6 (20–25)	6.5 (2–11.5)
12 mo	25.4 (20–30)	8.3 (2–12)
Serum drug levels (mg/L, mean and range) at		
3 mo	73.5 (56–86)	7.3 (1.3–15)
12 mo	76.8 (51.4–91)	8.1 (1.1–18)
Patients remaining in the trial (n, %) at		
3 mo	16 (84.2)	13 (68.4)
12 mo	16 (84.2)	13 (68.4)
Patients seizure free (n, %) at		
1 mo	10 (52.6%)	1 (5.3%)
3 mo	12 (63.1%)	7 (36.8%)
12 mo	13 (68.4%)	10 (52.6%)

VPA, valproic acid; LTG, lamotrigine.

diplopia, one; nervousness, one; increased appetite, one). Side effects were generally mild and transient and did not lead to drug withdrawal in any patient. In the LTG group, diplopia and headache persisted during the first 3 months of treatment. In the VPA group, body weight increased by about 3 kg (7.1% of body weight) in one boy during the first 2 months of treatment, but it did not increase thereafter.

DISCUSSION

Although in previous monotherapy trials, both VPA and LTG were reported to be effective in controlling clinical absence seizures and to reduce the frequency and duration of spike–wave discharges in children and adolescents (9,19,20), the present investigation is, to our knowledge, the first in which these drugs were directly compared in a head-to-head, controlled trial. Our findings show that VPA and LTG were associated with control of typical absence seizures in >50% of treated patients, although onset of efficacy was much faster with VPA. At 1 and 3 months, 5% and 37% of LTG-treated patients achieved seizure control, compared with 53% and 63%, respectively, of patients assigned to VPA. Although seizure control may be seen at low LTG doses, the slow titration phase required for this drug undoubtedly contributes to its lesser control rate in the short term. It should be stressed in this respect that our titration protocol, similar to that adopted by Frank et al. (9), used higher initial doses and faster dosage increments compared with the current guidelines, which are designed to minimize the risk of dose titration–dependent skin reactions (15). Although at 12 months, seizure-freedom rates were not significantly different in the two groups, more patients taking VPA achieved seizure freedom than than did those taking LTG (68% vs. 53%). Larger trials would be required to determine whether such a difference reflects a lower efficacy of LTG overall, or it is simply a chance finding associated with our limited sample size. Whether higher responses can eventually be achieved at VPA and LTG dosages higher than those used in this study also remains to be determined.

In the present trial, LTG efficacy at 3-month follow-up was somewhat less than that reported by Frank et al. (9) after an escalation phase of unclear duration (37% vs. 71%, respectively). Although Frank et al. (9) used dosages up to 15 mg/kg, only two of their 30 seizure-free patients responded at doses >10 mg/kg. The differences in responder rates between our study and the study of Frank et al. could be related to assessment methods, as it is unclear whether a 24-h EEG recording was required to meet the criteria for seizure freedom in the latter study. As to the early onset of VPA efficacy (52% at 1 month), our series is in agreement with other reports in the literature (1,2,18). With VPA, longer duration of treatment was associated with only a modest increase in responder rates over time (63% and 68% after 3 and 12 months, respectively).

Adverse side effects, which were generally mild and transient, occurred more frequently in the LTG group, in contrast with the suggestion that LTG may be better tolerated (15). Nonetheless, no patients were withdrawn from the study for safety-related reasons.

When selecting an agent to treat absence seizures, speedy onset of action is an important factor to be taken into consideration. Tolerability and safety considerations, however, also are important. Although with LTG, the risk of skin rashes and other hypersensitivity reactions is minimized by a slow titration, our study used a titration scheme faster than currently recommended (15), and our sample size was too small to assess risk of rare but serious side effects such as Stevens–Johnson syndrome. Although the slow onset of action is a clear drawback for LTG, this drug could be reasonably tried as initial therapy for typical absences in patients at risk of significant adverse effects from alternative agents such as VPA and ESM. For example, with VPA, hepatotoxicity in young children, weight gain in already obese patients, and risk of teratogenicity in older girls are significant concerns (21,22). LTG, together with ESM, also may offer an alternative to VPA in patients in whom the latter had been found to be ineffective or to paradoxically aggravate absence seizures (23).

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