Valproate Efficacy in Absence Seizures Is Hard to Beat: Lamotrigine Comes Close

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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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 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.

COMMENTARY

Ethosuximide and valproate (VPA) are drugs of choice for generalized absence seizures. For patients who have other seizure types, such as generalized tonic–clonic or myoclonic seizures, VPA is the only choice supported by clinical trials. There is a need for alternative agents, particularly for patients at high risk of adverse experiences from VPA, for individuals who are already overweight, and for female patients who are fertile or approaching childbearing age.

Several of the newer antiepileptic drugs (AEDs) have a wide spectrum of efficacy, with evidence of efficacy in absence seizures being mostly anecdotal. New AEDs that potentially are effective in absence seizures include felbamate, lamotrigine (LTG), topiramate, levetiracetam, and zonisamide. With the exception of LTG, these agents predominantly have been evaluated for add-on therapy in small case series of refractory patients (1–4). LTG appeared to be effective as an add-on treatment in patients with refractory absence seizures and as an initial monotherapy in small, open-label trials (5,6). In addition, one responder-enriched, placebo-controlled, double-blind trial was performed in 45 children (ages 3 to 15 years) with newly diagnosed typical absence seizures (7). The LTG dose was initially escalated to 7 mg/kg/day and, after enrollment, increased to 15 mg/kg/day in 20 patients. With this escalation, 71.4% became seizure free and qualified for randomization to placebo versus LTG, which was the next phase of the study. Twenty-eight patients were randomized and completed the trial. After randomization, only 64% of patients randomized to LTG remained seizure free (compared with 21% of patients randomized to placebo; $P < 0.02$). Thus the efficacy of LTG overall was less than suggested in the open-treatment phase. Nevertheless, LTG seemed to be a promising alternative for patients with absence seizures. A trial comparing LTG with established antiabsence agents was clearly needed.

Trials demonstrating superiority over placebo may be helpful for licensing authorities, such as the Federal Drug Administration, but trials comparing the new drug with an established one are more helpful to clinicians in determining AED choice in practice.

In the study by Coppola et al., 38 children with newly diagnosed typical absence seizures and the syndromes of childhood absence or juvenile absence epilepsy were randomized to a treatment with VPA or LTG. VPA efficacy was already obvious after 1 month of treatment, whereas LTG efficacy started to appear at 3 months. Even then, only 36.8% of LTG patients were seizure free, in comparison to 63.1% of patients taking VPA. The difference was not significant because of the small number of patients. At 1 year, the seizure-free rate for patients administered LTG and VPA was very similar (10 of 19 children taking LTG and 13 of 19 children taking VPA).

This study indicates that LTG is a treatment option for patients with absence seizures, although optimal efficacy is not to be expected immediately. However, the study by Coppola et al. does not suggest that LTG should become the drug of choice for absence seizures. VPA was very well tolerated, with fewer adverse events reported than in the LTG arm of the study over a 1-year period. In addition, this investigation was a small unblinded study, and a larger, preferably, blinded study, will be needed to confirm the results.

The Coppola et al. report does not establish whether LTG and VPA are effective in the same patients or whether they have complementary roles. In one study, eight patients, with typical absence seizures resistant to VPA or ethosuximide, became seizure free with LTG add-on therapy (5). Five of these patients were able to discontinue other AEDs, and absence seizures relapsed in only one patient. In another study, 64% of 15 patients resistant to VPA became seizure free after adding LTG (6). LTG does not share with VPA the mechanism of blocking the T-calcium current (8,9). Because it seems to have a different antiabsence mechanism than VPA, it possibly may be more effective in patients who are resistant to VPA—a hypothesis that could be tested in a crossover trial. The study by Coppola and colleagues excluded patients with syndromes that are known to be relatively resistant to VPA, such as eyelid myoclonia with absences and epilepsy with myoclonic absences. It would be helpful for future comparative trials to include these patients.

The identification of agents that are effective for absence seizures has lagged behind the process of determining effective medications for partial-onset seizures, yet trials to establish efficacy of new AEDs in absence seizures can be performed easily, particularly for drugs that do not require prolonged titration (10). Controlled, randomized trials for testing efficacy in absence seizures are needed for topiramate, levetiracetam, and zonisamide. Because absence seizures usually occur very frequently and are not thought to produce neuronal injury, a short placebo-controlled phase may be considered without ethical concerns. One potentially effective study design could be a double-blind trial, with one treatment arm receiving the study drug and the other treatment arm receiving placebo for 2 to 4 weeks and then VPA. Such a design may satisfy both licensing agencies and clinicians.

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