EPILEPSY CURRENTS

Current Literature

In Clinical Science

Treatment of Childhood Absence Epilepsy—An Evidence-Based Answer at Last!

Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy.

Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Capparelli EV, Adamson PC; Childhood Absence Epilepsy Study Group. *N Engl J Med* 2010;362(9):790–799.

BACKGROUND: Childhood absence epilepsy, the most common pediatric epilepsy syndrome, is usually treated with ethosuximide, valproic acid, or lamotrigine. The most efficacious and tolerable initial empirical treatment has not been defined. METHODS: In a double-blind, randomized, controlled clinical trial, we compared the efficacy, tolerability, and neuropsychologic effects of ethosuximide, valproic acid, and lamotrigine in children with newly diagnosed childhood absence epilepsy. Drug doses were incrementally increased until the child was free of seizures, the maximal allowable or highest tolerable dose was reached, or a criterion indicating treatment failure was met. The primary outcome was freedom from treatment failure after 16 weeks of therapy; the secondary outcome was attentional dysfunction. Differential drug effects were determined by means of pairwise comparisons. RESULTS: The 453 children who were randomly assigned to treatment with ethosuximide (156), lamotrigine (149), or valproic acid (148) were similar with respect to their demographic characteristics. After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar (53% and 58%, respectively; odds ratio with valproic acid vs. ethosuximide, 1.26; 95% confidence interval [CI], 0.80 to 1.98; P = 0.35) and were higher than the rate for lamotrigine (29%; odds ratio with ethosuximide vs. lamotrigine, 2.66; 95% CI, 1.65 to 4.28; odds ratio with valproic acid vs. lamotrigine, 3.34; 95% CI, 2.06 to 5.42; P < 0.001 for both comparisons). There were no significant differences among the three drugs with regard to discontinuation because of adverse events. Attentional dysfunction was more common with valproic acid than with ethosuximide (in 49% of the children vs. 33%; odds ratio, 1.95; 95% CI, 1.12 to 3.41; P = 0.03). CONCLUSIONS: Ethosuximide and valproic acid are more effective than lamotrigine in the treatment of childhood absence epilepsy. Ethosuximide is associated with fewer adverse attentional effects. (ClinicalTrials.gov number, NCT00088452.)

Commentary

The significance of the recent study by Glauser et al. from the Childhood Absence Epilepsy Study Group (1) can best be appreciated in its historical context. "Absence" as a term to describe seizures was introduced by Poupart in 1705 and was subsequently followed by the terms "petit mal" in 1838 and "pyknolepsy" in 1916 (2). Adie (1924) is credited with introducing the latter term into the English literature (3). This was not a trivial issue, because the word derived from the Greek denotes something that is "densely packed". Thus, the definition of pyknolepsy epilepsy extends beyond the discrete seizure type (absence) and directly implies frequency of the events. The description provided by Adie (with appropriate attribution to previous authors) contains the elements of what would become the syndrome of Childhood Absence Epilepsy (CAE). The semiology of the events is described as "an inhibition of the higher psychical processes lasting from 5–10 seconds…. The child sits or stands with limbs relaxed staring vacantly before him, the eyeballs may roll upwards, the lids may flicker, but there are no convulsive movements, and consciousness is never entirely lost. After the attack the child is well at once, and continues his interrupted game or task as if nothing had happened."(3) Key features described include: age of presentation between 4 and 10 years, frequency of 6 to 100 seizures per day, refractory to treatments available at the time and complete resolution with normal cognition in the setting of a previously normal child. The next major advance came in 1935 with the pioneering work of Gibbs et al., who reported that the semiology of pyknolepsy was correlated with a 3-Hz, generalized spike-wave pattern on the recently developed electroencephalogram (4). Thus, the constellation of features for CAE was defined and included semiology, seizure frequency, age of onset, prognosis and EEG correlate.

Despite the perceived benign nature of the syndrome, the need to provide children with symptomatic relief during the active phase of their epilepsy and the reality that not all children spontaneously stopped having seizures led to the use of available antiepileptic drugs (AEDs). The burgeoning field of medicinal chemistry identified a number of heterocyclic compounds

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with antiepileptic properties, including two, phenobarbital and trimethadione, that had some efficacy against absence seizures. The search for more efficacious agents with more tolerable adverse effect profiles led to the synthesis of methylphenyl succinimide in 1951(5), followed by ethosuximide (ESM; initially reported by its laboratory number, PM 671) in 1958 by Zimmerman and Burgemeister (6). In that initial report of ESM, 109 children with petit mal most of whom had failed previous medications, were observed. This is reminiscent of most current AED trials, in which patients who are refractory to currently existing AEDs are enrolled. The study design was retrospective, not randomized or blinded. The authors attempted to get a diagnostic EEG but could not do so in all cases and used seizure frequency (presumably reported by the family) as the baseline again which efficacy would be compared. Complete seizure freedom for the entire population was reported as 42% during an average duration of treatment of 44 weeks (range, 12–96 weeks). Another 24% achieved 80–99% reduction of seizures. The study population was then segregated into those having pure petit mal (pyknolepsy); mixed petit mal, which included minor motor movements; and petit mal combined with other types of seizures, specifically grand mal. It was reported that 61% of the pyknolepsy group had complete control, whereas those with mixed petit mal and/or psychomotor seizures had complete control rates in the 21–40% range. Of interest, the combination of pure petit mal and grand mal seizures had a seizure-free rate of 59%. This demonstrates the importance of precise specification of seizure types with regard to AED trial results.

In parallel with the recognition of the multiple seizure types associated with absence epilepsy was the appreciation of the role of the EEG in its diagnosis. The question of the duration of spike-wave bursts required to have a clinical correlate was answered by Holmes et al. (7) in a study that demonstrated that 80% of individuals had delayed reaction times at 0.5 seconds after a discharge. In addition, it was demonstrated that EEG-proven seizures were commonly missed by clinical observation alone (8, 9).

ESM was the primary medication for children with absence seizures until 1974, when the relatively new AED, valproic acid, was reported to have resulted in 100% seizure control in 12 of 17 individuals who had seizures characterized by absences with or without automatisms and who had an EEG that revealed a spike wave pattern (10). This led to a series of reports comparing ESM with valproic acid (VPA) (11–13). In 1982 Callaghan et al. (11) described a study in which patients with typical absence epilepsy (precise definition was not provided), with no other seizure types, and with a 3-Hz spike-wave EEG were randomized in a prospective fashion to receive either drug. Fourteen patients were assigned to each group, all but five of whom had 6 hours of EEG recording prior to treatment and every 6 months after treatment initiation. Medication doses were titrated according to reports of seizure recurrence by the families. Complete control was defined by no reports of seizures and no evidence of seizures on video EEG during a 6-month period, although details were not provided as to the occurrence of any epileptiform discharges. Adverse effects included pancreatitis and obesity in one patient each associated with VPA and drowsiness in one patient on ESM. Complete control was achieved in eight patients on ESM and in six on VPA. Although the numbers were small, this study demonstrated relative equivalency of the two medications in a homogeneous population of children with use of both clinical and EEG measures. Of note, the seizure-free rate was not 100% as described by Adie (3).

In the 1990s, a series of reports (14–16) indicated that lamotrigine (LTG) was also an effective agent in the treatment of absence epilepsies. This new AED had the benefits of a low adverse effect profile and efficacy against the generalized tonic-clonic seizures that sometimes accompany CAE. A randomized, open-label trial compared LTG to VPA (17). The study population included children age 3 to 13 years who had normal development and who were newly diagnosed with typical absence seizures that were correlated with generalized spike waves occurring within the frequency range of 2.5 to 4 Hz, occurring spontaneously or induced by hyperventilation. A total of 38 children were randomized to either group, and doses of medications were increased until adverse effects were noted or maximal milligram-per-kilogram doses of each were reached. Outcome was measured by report of seizure recurrence and presence of absences present on video EEG. Although approximately equal proportions of the VPA and LTG groups were seizure free at 1 year (68.4% and 52.6%, respectively), the authors note the delayed effect of the LTG, because the percentages of seizure control were 63.1% and 36.8% for VPA and LTG, respectively, at 3 months, in part reflecting the required slow titration of lamotrigine. Adverse effects were noted in approximately 10% of the VPA group and in 32% in the LTG group; none caused withdrawal from the study.

Although additional AEDs, including gabapentin (18), levetiracetam (19), zonisamide (20), topiramate (21), and stiripentol (22) have been reported in uncontrolled trials to have efficacy against absence seizures, ESM, VPA, and LTG have remained the most commonly considered treatment options for CAE. How, then, is one to make an informed decision regarding which medication is optimal for our patients? Evidenced-based treatment guidelines from the International League Against Epilepsy (23) using defined criteria for quality of evidence and recommendations indicated that ESM, VPA, and LTG could all be used as first-line therapy for absence epilepsy in childhood, because there were no firm data to determine which of these was the drug of choice. Expert consensus panels have reached slightly different recommendations, with ESM (24) selected by American epileptologists as the first AED for CAE, whereas European colleagues prefer VPA (25). Recent scholarly reviews present the current state of affairs. They first considered randomized clinical trials of the treatment of typical absence seizures (26) and concluded that they found "no reliable evidence to inform clinical practice. The design of further trials should be pragmatic and compare one drug with another." The second article (27) considered all available medications for absence epilepsy and concluded that they "found that a direct comparison of drugs a challenge because of different study populations, different study designs, and the relatively small number of patients included in the studies and case reports." They further commented that AED selection should be informed by adverse effect profiles and that, in the absence of high-quality evidence, "ESM, VPA and LTG are effective in the treatment of absence seizures."

It is against this backdrop that this study by Glauser et al. (1) should be considered. A total of 453 children were recruited from 32 sites in the United States. Strict inclusion and exclusion criteria (described in detail) were utilized, including the following: a diagnosis of CAE utilizing International League Against Epilepsy criteria, bilateral synchronous spike-wave discharges (2.7–5 Hz) that occurred on a normal background, and the recording of at least one electroclinical seizure lasting 3 seconds or more on a 1-hour video EEG. Additional criteria related to body size and normal serum chemistries. The patients were randomly assigned to ESM, VPA, and LTG groups in approximately equal numbers. Investigators, patients, and caregivers were blinded to the study medication. Neuropsychologic evaluation performed no later than 7 days after beginning study medication included the Connors Continuous Performance Test (CCPT), standardized neuropsychologic evaluation in multiple domains, behavior, and quality of life. The dose of each medication was increased empirically on the basis of seizure occurrence and lack of adverse effects. Dosage maxima were based on body weight (60 mg/kg/d ESM; 60 mg/kg/d VPA, 12 mg/kg/LTG). Clearly defined criteria for treatment failure included the following: clinical and/or electrographic seizures at weeks 16 or 20, one or more generalized tonic-clonic seizures, and multiple chemical (e.g., thrombocytopenia) and clinical (e.g., pancreatitis) toxicities. The primary outcome measures (freedom from treatment failure) at 16 weeks for each AED were as follows: ESM, 53%;VPA, 58%; and LTG, 29%. Thus, ESM and VPA were not significantly different, and both were superior to LTG. The secondary outcome measure (attentional dysfunction) revealed that VPA was more commonly associated with attentional problems as measured by the CCPT when compared with ESM at rates of 49% and 33%, respectively. This is an exemplary study with regard to its prospective, double-blind, randomized study design; stringent criteria for subject inclusion/exclsuion; utilization of EEG to determine seizure freedom; and clearly defined criteria for treatment failure. The study is perhaps unique in using AED effectiveness (seizure control and neuropsychologic toxicity) as the means to determine optimal therapy.

The major shortcomings of this study have been described in recent reviews (28, 29) and include the following: short study duration (20 weeks), uncertainty as to the clinical significance of the change in CCPT index, and the high VPA dose titration required, if clinically tolerable. These concerns are important and hopefully will be addressed by long-term follow-up of the study cohort. In addition, we may also learn about clinical and electrophysiologic predictors of continuation of absence and emergence of generalized tonic-clonic seizures. Serum was collected to determine AED concentrations, so perhaps genomic biomarkers of efficacy, adverse effects, and long-term outcome will also be forthcoming.

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