

Ezogabine treatment of childhood absence epilepsy

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ABSTRACT – Generalised-onset absence seizures can be resistant to treatment with currently available antiepileptic drugs. Ezogabine (retigabine), a potassium channel opener, is approved for the treatment of focal-onset seizures. This is a case report of an adult with childhood absence epilepsy whose daily absence seizures ceased with adjunctive ezogabine. A 59-year-old woman, with a history of typical absence seizures since the age of 6 years, had multiple seizures daily despite trials of over 11 antiepileptic drugs. While taking lamotrigine and zonisamide, ezogabine at 50 mg daily was added. The dose was slowly increased and once a total dose of only 200 mg/day was reached, she became seizure-free for three months. After subsequently discontinuing zonisamide, absence seizures returned. Further increasing the ezogabine to 400 mg/day, in addition to lamotrigine, did not restore seizure freedom, but adding back zonisamide at half dose again reduced their frequency. Ezogabine at low dose, added to lamotrigine and zonisamide, led to sustained absence seizure freedom. The return of seizures after zonisamide discontinuation suggests that the seizure freedom may have been the result of the different mechanisms of action of the antiepileptic drugs.

Key words: ezogabine, retigabine, absence seizure, childhood absence epilepsy, treatment, mechanism of action

Childhood absence epilepsy (CAE) is associated with typical absence seizures and a generalised spike-and-wave discharge of 2.5-4/second. Seizures spontaneously remit in CAE when many patients reach adulthood, but may persist in some patients. CAE is categorised into subtypes and, among these, variations have been identified in the genes *CACNA1H*, *GABRG2*, *GABRA1*, and *GABRB3* which encode T-type calcium channels and gamma-aminobutyric acid (GABA) receptors (Online Mendelian Inheritance in Man, 2013). This genetic

heterogeneity suggests that there may be multiple mechanisms by which antiepileptic drugs (AEDs) control seizures in CAE.

The Childhood Absence Epilepsy Treatment Study found that ethosuximide, compared to divalproex or lamotrigine, is presently the drug of choice for treatment of absence seizures (Glauser *et al.*, 2010). Ethosuximide has been shown to modify low-threshold T-type calcium currents in the thalamus (Coulter *et al.*, 1989). It has also been reported to decrease sodium and calcium-activated potassium currents in the

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thalamus and layer V cortical pyramidal neurons, and to reduce GABA levels in a genetic rat model of absence epilepsy (Gören and Onat, 2007).

Many patients have absences which are not controlled by ethosuximide, and a small number have absence seizures that are resistant to all current AEDs. Therefore, the identification of new AEDs which effectively control absence seizures is needed. We report, herein, the successful off-label treatment of an adult with CAE using ezogabine (retigabine [EZG]), a new AED which facilitates the opening of voltage-gated potassium channels (Faught, 2011).

Case study

A 59-year-old woman developed absence seizures at the age of 6 years. Her birth, growth, and development were normal. Epilepsy risk factors included a minor head injury and a grandmother who had “petit mal” seizures. Seizures had no warning and involved behavioural arrest and interruption of speech and thought. Triggers for seizures included sleep deprivation, stress, menses, being in a car whilst passing

trees with sunlight behind, and strobe lights. As a child and young adult, absence seizures were resistant to ethosuximide, methsuximide, phensuximide, phenytoin, phenobarbital, and the ketogenic diet. Seizures spontaneously stopped in her mid 20s. She was able to discontinue AEDs and have two healthy children.

At age 47, absence seizures recurred during emotional stress, due to a divorce and following a minor head injury. They occurred from 3 to 10 times a day and, for the first time, she had two generalised tonic-clonic seizures (GTCS) between 47 and 54 years of age, despite trials of lamotrigine, levetiracetam, and divalproex. Brain MRI was normal and 72-hour video-EEG monitoring recorded 151 clinical and subclinical seizures with generalised spike-and-wave complexes at 3/second in bursts lasting 5-38 seconds (*figure 1*). Subsequently, repeat trials of ethosuximide up to 500 mg TID, acetazolamide, and divalproex, as well as trials of zonisamide, rufinamide, topiramate, and lacosamide were ineffective at controlling absences and caused adverse effects.

Seizures were carefully counted daily for the two years prior to the current study, during which time she had an average of 19 seizure-free days per year, a

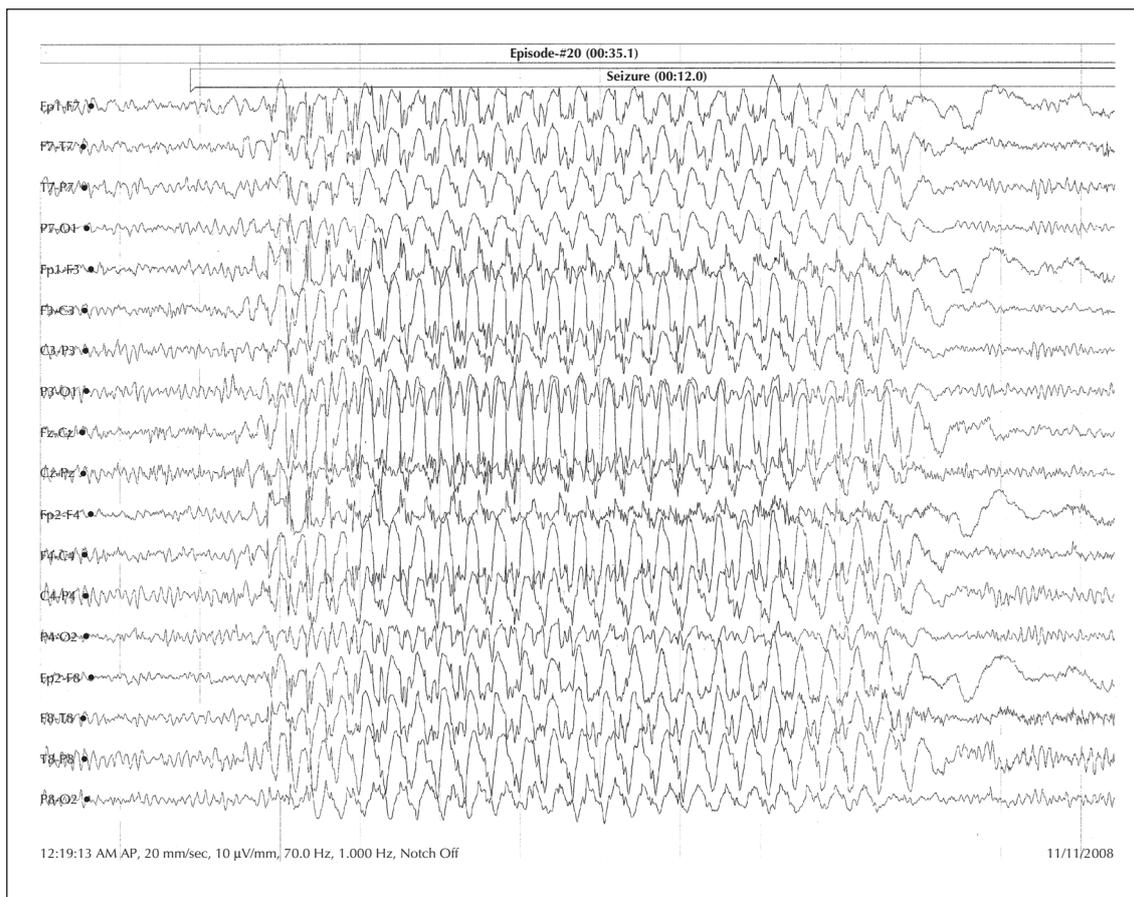


Figure 1. Ictal scalp EEG.

maximum seizure-free period of six days, and three more GTCS. Between the ages of 58-59, she averaged 2-3 absence seizures (range: 0-14) per day while taking lamotrigine 200 mg BID and zonisamide 200 mg BID. She was started on very low-dose ezogabine at 50 mg daily which was increased slowly by 50 mg/day increments on a TID schedule at 14 day intervals (*figure 2A*). Once reaching an ezogabine dose of 50 mg in the morning, 50 mg at midday, and 100 mg at night, her absence seizures stopped 11 days later (*figure 2B*). She continued ascending to a pre-planned ezogabine dose of 100/50/100 mg daily. With these three concomitant AEDs, she complained of cognitive difficulties, sedation, back pain, and somnolence, thus a taper of zonisamide was begun by decreasing 100 mg/day at ten-day intervals. She remained seizure-free, except for only one seizure, for a total of 91 consecutive days. Whilst off zonisamide, her cognition and back pain improved, but five days after her last dose of zonisamide, absence seizures recurred at a rate of 2-3

per day on ezogabine at 100 mg TID and lamotrigine at 200 mg BID. Ezogabine was gradually increased to a total daily dose of 400 mg, but absence seizures increased to 4-6 per day, thus it was lowered back to 100 mg TID and zonisamide was again added to this regimen. With adjunctive zonisamide at 200 mg per day, she again had many consecutive days of seizure freedom, but did have days with up to four absences. Nevertheless, the same adverse effects returned, so she elected to wean herself off and discontinue zonisamide treatment. Subsequently, clobazam was added to treatment with ezogabine and lamotrigine. Despite dose adjustments, seizure control was no better and she complained of muscle weakness, arthralgia, and confusion, thus ezogabine was stopped. No retinal or skin abnormalities were found.

Discussion

An adult with CAE who had multiple daily absence seizures, which were resistant to treatments with over 11 AEDs and the ketogenic diet, became essentially seizure-free after low-dose ezogabine was added to lamotrigine and zonisamide. Withdrawal of zonisamide (leaving the patient on low-dose ezogabine and lamotrigine at 200 mg BID) caused a return of absence seizures, which were reduced somewhat after reinstatement of half-dose zonisamide. These observations suggest that ezogabine, in combination with lamotrigine and zonisamide, may be an effective treatment of absence seizures.

Ezogabine, known by the generic name retigabine in Europe, is approved by the U.S. Food and Drug Administration (FDA) only for adjunctive treatment of adults with focal (partial)-onset seizures based upon the results of three randomised controlled trials (Porter *et al.*, 2007; Brodie *et al.*, 2010; French *et al.*, 2011). It has not been formally studied for generalised-onset seizures. In one ezogabine study, five patients were included (18% of the total) with generalised-onset seizures, but efficacy was only a secondary endpoint and the outcomes were not analysed relative to seizure type (Study 202; GlaxoSmithKline personal communication).

The mechanism of action of ezogabine is believed primarily to be based on its effect as a positive allosteric modulator of selected subtypes of potassium channels (Gunthorpe *et al.*, 2012). EZG predominantly binds the hydrophobic pocket in the gate region of the $K_v7.2-7.5$ channels (encoded by the *KCNQ2-5* genes). This essentially partially props open the gate which, as a result, allows these channels to more easily open in response to membrane depolarisation and to remain open longer (Faught, 2011). Opening of these channels enhances the outward potassium M current, which

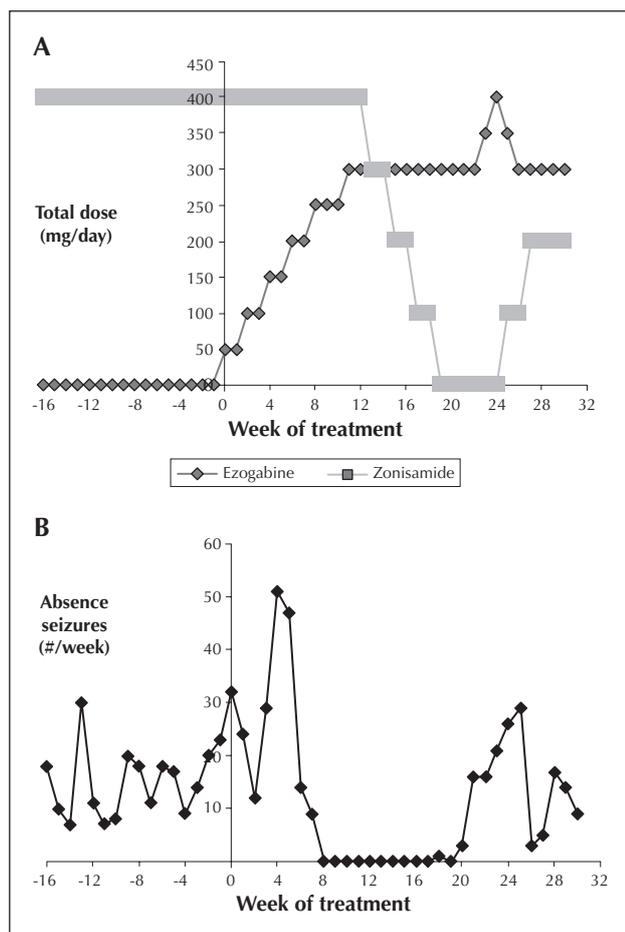


Figure 2. (A) Doses of ezogabine and zonisamide relative to weeks of treatment. Lamotrigine was maintained at a constant dose of 400 mg/day throughout this observation period. (B) Weekly absence seizure count relative to weeks of treatment.

in turn stabilises the resting and sub-threshold membrane potential.

Lamotrigine, has a mechanism of action that is believed to include enhancement of rapid inactivation of voltage-gated sodium channels, thereby decreasing the release of excitatory neurotransmitters, especially glutamate. It is FDA-approved for the treatment of focal-onset seizures, seizures in Lennox-Gastaut syndrome, and also GTCS in primary (genetic) generalised epilepsy.

Zonisamide is FDA-approved for treatment of focal-onset seizures in adults, but has been used to treat generalised seizures. Its mechanisms of action are believed to be the: 1) enhancement of rapid inactivation of sodium channels; 2) decrease of voltage-dependent transient inward (T-type) calcium currents; 3) binding of the GABA-benzodiazepine ionophore; and 4) mild inhibition of carbonic anhydrase, as well as others (Vossler, 2010).

It is suspected that ezogabine alone was not responsible for absence seizure freedom because seizures returned quickly after zonisamide was discontinued. Rather, it seems likely that the different mechanisms of action of these three AEDs worked together to control this patient's seizures. For example, lamotrigine and zonisamide likely enhanced rapid inactivation of sodium channels, possibly with effects on T-type calcium currents and the GABA ionophore, and ezogabine enhanced potassium channel opening. Conversely, one could argue that the return of absence seizures after zonisamide withdrawal was not due to the removal of its positive effects, but rather due to the development of ezogabine drug resistance. Against this argument are the observations that higher-dose ezogabine did not restore seizure control and that reinstatement of half-dose zonisamide did again partially improve seizure control.

Our case has at least two implications for the treatment of absence seizures. One is that adjunctive AED therapy may be more successful than monotherapy in some cases of resistant CAE. The second is that

further research on the treatment of CAE with AEDs with unconventional mechanisms of action may be indicated. □

Disclosures.

Dr. Vossler in the past has served as a speaker and site investigator for GlaxoSmithKline. This study had no financial support.

References

- Brodie MJ, Lerche H, Gil-Nagel A, *et al.* Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010; 75: 1817-24.
- Coulter DA, Huguenard JR, Prince DA. Characterization of ethosuximide reduction of low-threshold calcium current in thalamic neurons. *Ann Neurol* 1989; 25: 582-93.
- Faught E. Ezogabine: a new angle on potassium gates. *Epilepsy Curr* 2011; 11: 75-8.
- French JA, Abou-Khalil BW, Leroy RF, *et al.* Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology* 2011; 76: 1555-63.
- Glauser TA, Cnaan A, Shinnar S, *et al.* Ethosuximide, valproic acid and lamotrigine in childhood absence epilepsy. *New Engl J Med* 2010; 362: 790-9.
- Gören MZ, Onat F. Ethosuximide: from bench to bedside. *CNS Drug Rev* 2007; 13: 224-39.
- Gunthorpe MJ, Large CH, Sankar R. The mechanism of action of retigabine (ezogabine), a first-in-class K⁺ channel opener for the treatment of epilepsy. *Epilepsia* 2012; 53: 412-24.
- Online Mendelian Inheritance in Man. <http://www.omim.org/entry/600131?search=childhood%20absence%20epilepsy&highlight=absent%20absence%20epilepsy%20epileptic%20childhood>, accessed 14 December 2013.
- Porter RJ, Partiot A, Sachdeo R, Nohria V, Alves WM, on behalf of the 205 Study Group. Randomized, multicenter dose-ranging trial of retigabine for partial-onset seizures. *Neurology* 2007; 68: 1197-204.
- Vossler DG. Zonisamide as adjunctive therapy for adults with partial-onset epileptic seizures: an efficacy and safety review. *Clinical Medicine Insights: Therapeutics* 2010; 2: 1-9.