New antiepileptic medication linked to blue discoloration of the skin and eyes

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Abstract: Ezogabine is an antiepileptic medication approved in June 2011 by the US Food and Drug Administration (FDA) as an adjunctive treatment for partial seizures. Minimal drug interactions and a novel mechanism of action made ezogabine an appealing new treatment option. However, adverse effects reported during clinical trials and following drug approval have been alarming. A Risk Evaluation Mitigation Strategy (REMS) program has been established for urinary retention. A safety alert was published in April 2013 warning ezogabine may cause retinal pigment abnormalities and/or blue-gray discoloration, most notably on or near the lips, nail beds, sclera and conjunctiva with long-term use. In October 2013, the FDA announced a formal label change to ezogabine to include a black boxed warning emphasizing the previously reported warnings of eye and skin discoloration and permanent vision changes. Given the unknown nature of the pathophysiology, consequences and potential for reversibility of these effects, GlaxoSmithKline and the FDA have published recommendations for patients currently receiving ezogabine. Further data from published case reports and long-term safety trials in the future may lend additional insight into these concerning effects.

Keywords: antiepilepsy medication, ezogabine, seizure, skin discoloration

Introduction

Epilepsy is a condition characterized by recurrent, excessive and unpredictable discharges of neurons within the brain that disturb normal brain function [Fisher *et al.* 2005]. Epilepsy manifests from various structural brain modifications which increase susceptibility for future seizures [Fisher *et al.* 2005]. It can be further defined as having at least 2 unprovoked seizures more than 24 hours apart, 1 unprovoked seizure similar in nature after 2 unprovoked seizures, or any 2 seizures in the context of reflex epilepsy. Data from epidemiological studies reveal that 20–40% of patients with newly diagnosed epilepsy will become refractory to available medical treatments, stressing the importance of continued development of new antiepileptic agents [French, 2007].

Seizures may be classified as generalized or focal based upon origination [Blume *et al.* 2001; Berg *et al.* 2010]. Ezogabine is an antiepileptic medication granted US Food and Drug Administration (FDA) approval in June 2011 for focal seizures in

adults greater than 18 years of age. While known internationally by the nonproprietary name retigabine, the US has adopted the generic name ezogabine.

Pharmacology

Broadly, antiepileptic medications can be divided into two groups: those medications that decrease neuronal excitation and those that potentiate neuronal inhibition. Ezogabine stabilizes neuronal potassium channels (Kv7.2–7.5) in the open position, thereby causing hyperpolarization and reduced firing of high-frequency action potentials [Faught, 2011; Gunthorpe *et al.* 2012; Jankovic and Ilickovic, 2013; Verma *et al.* 2013; GlaxoSmithKline, 2011]. Potassium channels Kv7.2–7.5 are distributed throughout the brain, making inhibition a useful target for seizure prevention [Maljevic *et al.* 2010; Owen, 2010]. Potassium channels Kv7 subtypes play a role in smooth muscle expression throughout the body [Jepps *et al.* 2013]. Further expression of these channels in the epithelium of the urinary tract explains certain ezogabine adverse effects [Streng

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et al. 2004]. Potassium Kv7 subtypes have also been studied in guinea pigs [Afeli *et al.* 2013] and rats [Reilly *et al.* 2013]. However, ezogabine does not target potassium channels in the heart, which are subtype Kv7.1 [Gunthorpe *et al.* 2012]. *In vitro* studies demonstrate ezogabine may reduce seizure activity by augmenting γ -aminobutyric acid (GABA) mediated neurotransmission as well [Streng *et al.* 2004]. This novel mechanism of action differs from the actions of other antiepileptic medications at sodium, calcium, glutamate and chloride channels, providing a unique option for those with medically intractable seizures [Gunthorpe *et al.* 2012].

Ezogabine is not metabolized *via* cytochrome P450 or P-glycoprotein pathways, allowing for a favorable drug interaction profile and predictable drug concentrations when used with most other antiepileptic medications [Tompson and Crean, 2014]. Ezogabine is metabolized through *N*-glucuronidation and *N*-acetylation. It is not known to interact with the cytochrome P450 enzyme systems and thus it does not have the significant drug interactions of many of the other antiepileptic medications. It has one active metabolite known as NAMR (retigabine *N*-acetyl metabolite). Ezogabine is 85% excreted by the kidney and about 14% in feces. The elimination half-life is approximately 7 hours and is prolonged in the elderly by up to 30%; thus a dose reduction is recommended in person older than 65 years [Owen, 2010; Tompson and Crean, 2013; GlaxoSmithKline, 2011].

Ezogabine is dosed 3 times daily (TID) and should be initially titrated from 100 mg to 400 mg. Clinical trials revealed limited additional benefit in terms of seizure control, but did see an increase in side effects associated with the 400 mg dose compared with the 300 mg dose. The maintenance dosage range is 200–400 mg TID [Owen, 2010; Harden, 2012].

Ezogabine can inhibit digoxin clearance, so additional monitoring of serum digoxin levels may be necessary. Up to a 30% decrease in ezogabine concentrations can be seen with concomitant phenytoin or carbamazepine administration. Ezogabine may enhance the QT prolongation properties of those medications that have a propensity to prolong the QT interval. It is recommended to avoid the combination when possible. Alcohol yields a 23% increase in ezogabine concentration, though the clinical effect is generally tolerated [Crean and Tompson, 2013; Tompson and Crean, 2013; GlaxoSmithKline, 2011].

Adverse effects

Pre-approval studies revealed a number of unique side effects associated with ezogabine. The novel, but nonselective, mechanism of action has led to the establishment of a Risk Evaluation Mitigation Strategy (REMS) for urinary retention. Ezogabine targets potassium channels located in the central nervous system as well as in the smooth muscle of the bladder. This may reduce the contractility of the bladder smooth muscle, resulting in urinary retention, hesitation and dysuria [Streng *et al.* 2004; Faught, 2011]. Close monitoring is required in patients with benign prostatic hypertrophy, cognitive impairment, and those taking anticholinergic medications. Additional side effects include a mean QT interval prolongation of 7.7 ms in healthy subjects, dose-related dizziness (32%) and somnolence (27%), and neuropsychiatric symptoms, including confusion (16%), fatigue (15%), psychotic symptoms (2%) and hallucinations (2%). Similar to other antiepileptic medications, ezogabine may increase suicidal ideation and provoke withdrawal seizures if it is not tapered over at least 3 weeks [Brodie *et al.* 2010; GlaxoSmithKline, 2011].

Euphoria-related adverse effects were seen in 6–9% of patients taking ezogabine in phase I clinical trials. Human abuse potential studies showed similar responses to ezogabine as those with benzodiazepines. However, ezogabine was deemed a lower abuse risk when considering the adverse effect profile and data from animal behavior studies. Considering similar rates of euphoria are seen with the other Schedule V antiepileptic medications, pregabalin and lacosamide, ezogabine was also designated a Schedule V medication [US Environmental Protection Agency, 2011].

Safety

A safety alert was published by the FDA in April 2013 which describes unique adverse effects not documented in 3 phase III clinical trials conducted in 512 total patients for 16–18 weeks [Porter *et al.* 2007; Brodie *et al.* 2010; French *et al.* 2011; Garin Shkolnik *et al.* 2014]. The alert warned ezogabine may cause blue-gray discoloration, most notably on or near the lips, nail beds, sclera and conjunctiva; however, more extensive involvement on the face and legs has also occurred. Patients reporting this abnormality were enrolled in ezogabine clinical trials, with an incidence of 6.3% (38 of 605 patients) and 95% of cases occurring after 2 years of treatment (mean 4.04

years, range 0.8–7 years). In October 2013, the FDA revised the label for ezogabine to include a black boxed warning emphasizing the serious risks of permanent skin and eye discoloration [US Food and Drug Administration, 2013].

Retinal pigment abnormalities concerning for vision loss were also associated with ezogabine use. This event was seen in approximately a third (11 of 36) of patients enrolled in ezogabine clinical trials who underwent eye examinations. Retinal abnormalities did not always occur in conjunction with skin, sclera or conjunctival pigmentation, and were only reported in patients who had been taking ezogabine for at least 3 years. Neither dermal nor ophthalmic adverse effects were noted in open-label extension studies of two phase III ezogabine clinical trials [Gil-Nagel *et al.* 2012; Biton *et al.* 2013]. Unfortunately, pathophysiology, consequences and reversibility potential are currently unknown and involvement may be more extensive than current case reports. Formal data beyond that provided in the safety alert have not yet been published.

Garin Shkronik and colleagues have reported 2 cases of blue-gray discoloration in 2 women who had been treated with ezogabine for more than 5 years. Skin discoloration had been present for at least 2 years. One patient discontinued ezogabine and had improvement in the skin discoloration, while the other patient continued on therapy [Garin Shkronik *et al.* 2014]. No further cases have been reported. Further case reports may provide additional insight into potential aggravating factors or consequences of these adverse effects. Currently, extensions of three premarketing phase III clinical trials are being conducted to evaluate the long-term safety of ezogabine, while two studies are in the recruitment phase to evaluate urinary voiding function and safety in patients of Asian heritage who have partial onset seizures.

Amiodarone, an antiarrhythmic medication, is also known for causing a blue-gray pigmentation of the skin with ultraviolet (UV) exposure, depending on both the dose and duration of therapy. Discontinuation of amiodarone leads to complete resolution of the skin pigmentation [Ammann and Braathen, 1996]. Minocycline, a tetracycline antibiotic commonly used for acne and rosacea, has been shown to cause blue-gray skin pigmentation in 15% of patients in one study [Dwyer *et al.* 1993; Morrow and Abbott, 1998]. Additionally, case reports have noted pigmentation of the sclera

associated with long-term minocycline use [Sabroe *et al.* 1996; Geria *et al.* 2009]. The pigmentation changes were noted in patients who had received minocycline for a minimum of 3 years, similar to the skin pigmentation changes noted with long-term ezogabine use [Geria *et al.* 2009].

Recommendations

Now that GlaxoSmithKline and the FDA are aware of the potential for blue discoloration associated with ezogabine use, a number of recommendations about future use have been released. These recommendations include:

- Asymptomatic patients do not need to discontinue the medication.
- All patients should receive a baseline eye exam, followed by eye exams every 6 months.
- All patients with ophthalmic changes should discontinue the medication.
- Patients with skin changes should seriously consider a substitute medication.

Patients should not discontinue ezogabine without talking to their healthcare provider first to prevent increased seizure frequency. Initiation of ezogabine should be avoided unless it is determined that the benefit of potentially enhanced seizure control outweighs the unknown risks of long-term use.

Healthcare providers are encouraged to report adverse events involving ezogabine to the FDA MedWatch program (www.fda.gov/MedWatch/report.htm).

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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