Ezogabine (retigabine)
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Introduction

Historical note and terminology

Ezogabine, a K channel opener used for treatment of partial-onset seizures in adults, was developed by Valeant Pharmaceuticals and GlaxoSmithKline. In 2011, it was approved by the European Medicines Agency under the trade name Trobalt and by the FDA, under the trade name Potiga. The drug is known as "ezogabine" in the United States and "retigabine" elsewhere. In the fall of 2016, GlaxoSmithKline, the manufacturer of Trobalt (retigabine) announced that this drug will be discontinued and will no longer be commercially available after June 2017. This is due to the very limited use of the drug and the continued decline in new patients being prescribed. Healthcare professionals were advised to begin seeking alternative medicines for existing patients as soon as possible and to ensure that all patients are withdrawn at the latest from this medicine by the end of June 2017. There is no approved generic version of Potiga or Trobalt.

Pharmacology

Ezogabine is an ethyl N-{(2-amino-4-[(4-fluorophenyl)methylamino]phenyl}carbamate. Ezogabine exerts an anticonvulsant effect by primarily opening neuronal voltage-gated, potassium-gated ion channels resulting in resting membrane potential stabilization—an action not shared by any of the other approved antiepileptic drugs.

Pharmacodynamics. Ezogabine acts on voltage-sensitive neuronal-specific outward potassium current that decreases neuronal excitability (Rheims and Ryvlin 2012). It binds to the key potassium channels: Kv7.2 to Kv7.5. Activity of ezogabine has been demonstrated across a broad spectrum of animal models of seizures, including generalized tonic-clonic, primary generalized, and partial seizures (Large et al 2012). Ezogabine is a subtype selective modulator of GABA(A) receptors with preference for extrasynaptic δ-containing receptors, which may explain its broad effectiveness as an antiepileptic and its lack of effect on absence seizures (Treven et al 2015). Its broad spectrum of anticonvulsant effects in animal models indicate that ezogabine could be useful in treating human epilepsy beyond complex partial seizures, but this remains to be proven. Ezogabine has shown neuroprotective properties in various models of neurodegeneration, but this is not significant in terms of epileptogenesis.

Because Kv7 channels are present on axons of unmyelinated, nociceptive, peripheral human nerve fibers, it is likely that activation of these channels by ezogabine may reduce the ectopic generation of action potentials in neuropathic pain (Lang et al 2008). This is the basis for considering its use for treating neuropathic pain.

Pharmacokinetics. Absolute oral bioavailability of ezogabine relative to an intravenous dose is approximately 60%. Ezogabine is rapidly absorbed and has linear, dose-related kinetics across the therapeutic dose range of 600 to 1200 mg/day (Owen 2010). It is approximately 80% bound to plasma protein and has a plasma half-life of 6 to 10 hours. The steady state volume of distribution of ezogabine is 2 to 3 l/kg following intravenous dosing. It is not metabolized by the cytochrome P450 system but by N-glucuronidation and N-acetylation. One acetylated metabolite, AWD-21-360, has minor activity as an anticonvulsant. Elimination of ezogabine occurs via a combination of hepatic metabolism and renal excretion. Therefore, plasma clearance of retigabine decreases as severity of renal or hepatic impairment increases. No adjustment of dose of ezogabine is required for gender, race, or genetic/polymorphisms (Tompson and Crean 2013).

Formulations. A sustained-release formulation of ezogabine is in development, which might address the inconvenience of its 3-times-daily dosing schedule and improve compliance. Structural modification by incorporation of a propargyl group significantly improves the brain distribution of ezogabine (Zhou et al 2015).

Clinical trials

Table 1. Clinical Trials of Ezogabine

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<th>Trial design</th>
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A multicenter, randomized, double-blind, placebo-controlled trial of ezogabine titrated to daily doses of 600, 900, or 1200 mg for 2 to 6 weeks as an adjunct for treatment of partial-onset seizures.

The responder rate was 33% for 1200 mg/day dose vs. 16% for placebo (Porter et al 2007).

A multicenter, randomized, double-blind, placebo-controlled trial in adults with partial-onset seizures receiving 1 to 3 antiepileptic drugs. Ezogabine titrated to 600 or 900 mg/d was continued for 12 weeks.

Study provided Class II evidence that adjunctive ezogabine reduced the occurrence of seizures in refractory partial epilepsy (Brodie et al 2010).

RESTORE 1 was a multicenter, randomized, double-blind, parallel-group trial to determine efficacy of ezogabine as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization.

This study provided Class II evidence that ezogabine at a dose of 1200 mg/day was effective with a responder rate of 55.5% vs. 22.6% in placebo (French et al 2011).

In open-label extensions of 3 clinical trials, persistence of the efficacy of ezogabine was maintained over an evaluation period of at least 12 months. Interim results of 2 open-label extension studies that assessed ezogabine safety and tolerability for partial-onset seizures showed that a reduction in seizure frequency from baseline (53%) and responder rate (52.5%) was maintained in patients on continuous 6-month therapy, whereas 12-month seizure-free rates were 13.1% and 7.1%, respectively (Gil-Nagel et al 2012).

A review of the results of 8 clinical trials of ezogabine, including 5 phase I and 3 phase III, shows that ezogabine is safe and effective as an adjunctive agent in patients with pharmaco-resistant partial seizures, but its precise role in the management of patients with epilepsy remains to be determined (Yamada and Welty 2012). A systematic review of controlled clinical trials of ezogabine, and comparison with similar trials of eslicarbazepine acetate, lacosamide, pregabalin, tiagabine, and zonisamide, showed a risk/benefit profile similar to that for comparator antiepileptic drugs (Martyn-St James et al 2012).

In open clinical trials using a flexible dosing regimen, ezogabine was effective as adjunctive therapy to carbamazepine/oxcarbazepine, lamotrigine, levetiracetam, or valproic acid in adults with partial-onset seizures (Lerche et al 2015).

A phase 3, randomized, double-blind, placebo-controlled, parallel-group study of ezogabine was conducted at 26 centers in Asia on patients with drug-resistant partial-onset seizures, and the results regarding efficacy and adverse effects were similar to those from previous studies on Caucasian patients (Lim et al 2016).

**Indications**

Ezogabine is approved by the FDA for the adjunctive treatment of partial-onset seizures in patients aged 18 years and older. It is approved by the European Medicines Agency for the adjunctive treatment of partial-onset seizures with or without secondary generalization in adults aged 18 years and older who have epilepsy.

**Off-label and investigational uses:**

- It is postulated that ezogabine could be effective in a rare form of neonatal epilepsy, benign familial neonatal convulsions, due to a mutation in KCNQ2 or KCNQ3, which code for Kv7.2 and Kv7.3, respectively (Stafstrom et al 2011).
- Addition of ezogabine to lamotrigine and zonisamide with titration of its dose helped to fully control seizures in an adult with history of absence epilepsy since childhood (Vossler and Yilmaz 2014). A retrospective study has provided class IV evidence that ezogabine is effective for refractory seizures in patients with epilepsy due to KCNQ2 encephalopathy (Millichap et al 2016).
- Ring chromosome 20, a genetic disorder with seizures, is a potassium channelopathy that is considered to be responsive to treatment with ezogabine (Walleigh et al 2013).
- Ezogabine may prove to be an effective antidystonic drug (Richter et al 2006).
The inhibition by ezogabine of psychostimulatory effects of cocaine, methylphenidate, and phencyclidine in rats indicate its potential in the treatment of addiction (Hansen et al 2007).

Contraindications

Patients may experience hypersensitivity to the active substance or to any of the excipients used in ezogabine.

Goals and duration of treatment

The aim as with any other antiepileptic drug is control of seizures. The longest duration of treatment in clinical trials was approximately 1 year. Some of the patients have been under treatment for longer periods, but the results have not been analyzed.

Dosing

The maximum total daily starting dose of ezogabine is 300 mg (100 mg, 3 times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. An effective maintenance dose is expected to be between 600 and 1200 mg/day.

Special considerations

Ezogabine and its metabolites are eliminated principally by renal excretion. No dose adjustment is required in patients with mild renal impairment, but a 50% reduction in the initial and maintenance dose of ezogabine is recommended in patients with moderate or severe renal impairment.

Pediatric. The safety and efficacy of ezogabine in children younger than 18 years of age have not been established yet. In a clinical study, pharmacokinetics of ezogabine across the dosage range of 100 to 300 mg 3 times a day as adjunctive therapy in adolescents with uncontrolled partial-onset seizures were consistent with observations in adult, but there were no conclusions regarding the safety or efficacy of the drug in this patient population due to small sample size as well as the short duration of study (Tompson et al 2016).

Geriatric. There are only limited data on the safety and efficacy of ezogabine in patients aged 65 years and older. A reduction in the initial and maintenance dose of ezogabine is recommended in elderly patients. Total daily dose is not recommended to exceed 900 mg.

Pregnancy. There are no adequate data from the use of ezogabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses. In a developmental study in rats whose mothers were treated with ezogabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known. Ezogabine is not recommended during pregnancy or in women of childbearing age who are not using contraception. It is unknown whether ezogabine is excreted in human breast milk.

Anesthesia. Ezogabine may increase the duration of anesthesia induced by some anesthetics, eg, thiopental sodium.

Interactions

Interactions of ezogabine with other antiepileptic drugs are minimal. Ezogabine does not interact with pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol; dose of either does not need to be altered when co-administered (Crean et al 2013). N-acetyl metabolite of ezogabine inhibits P-glycoprotein-mediated transport of digoxin in a concentration-dependent manner, indicating that it may inhibit renal clearance of digoxin. Administration of ezogabine at therapeutic doses may increase digoxin serum concentrations.

Adverse effects

Adverse events most commonly reported in clinical trials (dizziness, somnolence, headache, and fatigue) were dose-related due to effect on the CNS. Skin discoloration has been reported in cases as blue pigmentation, predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs
may also occur. There is a concern that this discoloration could be permanent. However, a case of ezogabine-induced skin discoloration that appeared 5 years after start of treatment resolved completely after discontinuation (Mathias and Abou-Khalil 2017). Pigmentary changes in the macula on fundus examination has been reported, and characteristics on imaging can guide ophthalmologists when they perform the FDA-recommended 6-month screening visits for ocular toxicity due to ezogabine. In 1 patient who presented with new retinal pigment abnormalities in the maculas of both eyes 9 months after starting ezogabine, there was partial resolution of the abnormalities after cessation of the drug (Zaugg et al 2017).

References cited


Mathias SV, Abou-Khalil BW. Ezogabine skin discoloration is reversible after discontinuation. Epilepsy Behav Case 2017;7:61-3. PMID 28417066


Owen RT. Ezogabine: a novel antiepileptic as adjunctive therapy for partial onset seizures. Drugs Today (Barc) 2010;46(11):815-22. PMID 21225020


Zaugg BE, Bell JE, Taylor KY, Bernstein PS. Ezogabine (Potiga) maculopathy. Retin Cases Brief Rep 2017;11(1):38-43. PMID 26909536


**References especially recommended by the author or editor for general reading.

**Other pertinent drugs**

Carbamazepine
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenytoin
Rufinamide
Tiagabine
Topiramate
Valproic acid
Vigabatrin
Zonisamide

**Other topics to consider**

Anticonvulsants
Benign familial neonatal seizures
Epilepsy
Ion channels and neurologic disorders
Pain
Pharmacological treatment of epilepsy in adolescents and adults
Neuropathic pain: treatment
Neuropharmacology