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Ezogabine: A New Angle On Potassium Gates

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Ezogabine is a new drug for adjunctive therapy of partial-onset seizures with a novel mechanism of action. As a potassium-channel facilitator, it promotes membrane repolarization and thus opposes rapid repetitive discharges. Side effects are typical for antiepileptic drugs and the safety profile is good. Occasional instances of urinary difficulty may require surveillance.

Ezogabine (EZG) is the nonproprietary name adopted in the U.S. for retigabine, the international nonproprietary name for (*N*- [2-amino-4-(4-fluorobenzyl amino) -phenyl] carbamic acid ethyl ester. In January 2011 approval for marketing in Europe under the brand name Trobalt[®] was recommended by the Committee of Medicinal Products for Human Use of the European Medicines Agency, with an indication for adjunctive treatment of partial-onset seizures, with or without generalization, for patients 18 years of age and older (1). It has been submitted for approval in the United States. The original developer in Dresden, Germany, found it as one of a family of aminopyrroles with anticonvulsant activity. Since initial reports in the mid-1990s (2), EZG has followed a long and winding course toward regulatory approval (3). This was less because of issues intrinsic to the drug and more because of shifts in corporate licensing. EZG is of particular interest because of its unique mechanism of action as a potassium-channel facilitator.

Animal Data

EZG was effective in a wide variety of animal models when tested in the NIH antiepileptic drug development (ADD) program and by the original manufacturer (4). It is active against seizures in rodents induced by maximal electroshock, pentylenetetrazole, picrotoxin, NMDA (2), and amygdalar kindling (5). Based on rotorod testing, it had a better protective index in these models than valproate or phenytoin (5). Thus it appeared to be a broad-spectrum drug when it emerged from preclinical testing. Subsequently, it has been found to be effective in the amygdala-kindled lamotrigine-resistant rat model of drug-resistant epilepsy (6), a model which is also resistant to phenytoin and carbamazepine.

Mechanism of Action

Ezogabine is often referred to as a “potassium channel opener”, but this is a simplified description. EZG does not directly open a potassium channel. The channels at which it acts are voltage-gated, not ligand-gated. This is demonstrated by its efficacy in the low-magnesium seizure model, which does not depend upon synaptic transmission (7). The principal mechanism by which membrane repolarization occurs after an action potential is an outward potassium current, termed the M-current (muscarinically-modulated). This current flows at subthreshold voltages and is enhanced as depolarization further opens the $K_v7.2$ and $K_v7.3$ species of voltage-gated potassium channels, allowing potassium to flow outward driven by its concentration gradient (8). EZG facilitates the action of the neuronal $K_v7.2$ and $K_v7.3$ channels (encoded by genes *KCNQ2* and *KCNQ3*) by shifting the channels’ activation potentials 20-30mV toward hyperpolarization (9). This has the following physiological consequences: 1) a lesser degree of depolarization is needed to open the channel; 2) the channel, which usually opens rather slowly, opens faster, and 3) the channel stays open longer- perhaps as much as two to four times longer(10). This presumably has the effect of slowing repetitive firing, and thus underlies the compounds’ antiseizure effect.

At the stereochemical level, EZG seems to act as a sort of prop or doorstop, binding into a hydrophobic pocket within the “gate” region of the $K_v7.2$ and 3 channels which is the site of a molecular “hinge”(11). To extend the analogy, once EZG has lodged within this pocket, it bends the hinge slightly open, decreasing the angle through which the gate must swing to open fully. Therefore less energy is required to open the channel and to keep it open. It should be noted that the gate must be slightly open for EZG to act, suggesting that its most important effect is to stabilize the channel in the open state- in a sense, propping it open at a more favorable angle (12). EZG does not affect cardiac potassium channels, possibly because those channels (e.g. $K_v7.1$; coded by gene *KCNQ1*) are missing a glycine component which is essential for EZG to fit within its target (11).



There were early reports that EZG increases GABA action and decreases glutamate release (13), but it now seems likely that these are epiphenomena.

Pharmacokinetics

EZG is rapidly absorbed, with a T_{max} of 1.5 hours, and absorption is delayed but not reduced by food (14). Serum concentrations are linear through 1200 mg/day. The elimination half-life is 8 hours, so in clinical trials it was given three times per day. EZG is mostly glucuronidated rather than being metabolized by cytochrome P450 enzymes; therefore no significant age or sex effects on metabolism are expected. No clinically significant drug interactions have been identified. Phenytoin and carbamazepine increase the metabolic rate of EZG modestly but phenobarbital does not (15). Both the parent drug and metabolites are renally cleared.

Efficacy

Results of two multinational, randomized, controlled trials of EZG in patients with refractory partial-onset seizures have been published (16,17). A third trial, enrolling mostly in the US, was recently reported (18). All three multicenter trials had a classical add-on design. The three most common concomitant drugs were carbamazepine (about half of patients), lamotrigine and valproic acid (about one-quarter each). Over 70% of patients were on polytherapy when EZG was added, so no conclusions were possible concerning the best combinations.

To sum up the efficacy results from these trials, there was a reduction in seizures in the tested dose range 600 to 1200 mg/day.

All data that follow are presented as the result for each dosage cohort with the result for the parallel placebo cohort subtracted. The key primary endpoint aimed at FDA approval was the responder rate for the intent-to-treat population (50% seizure reduction from baseline) calculated from baseline, including the titration period. For the 600 mg/day dose, this reduction exceeded the placebo reduction by 7% (16) and 12% (17), for 900 mg/day by 16% (16) and 28% (17), and for 1200 mg/day, 17% (16) and 27% (18). The key primary endpoint aimed at European Medicines Agency approval was the responder rate in the intent-to-treat (ITT) population during the maintenance (stable dose) period. This was, for the 600 mg/day dose with the placebo rate subtracted, 1% (16) and 2% (17), for the 900 mg/day dose 9% (16) and 14.5% (17), and for the 1200 mg/day dose 15.2% (16) and 33% (18). In the first study, these figures were lowered by the unusually high placebo responder rate of 26% during the maintenance period (16).

The secondary endpoint in these studies was the median percent seizure reduction over baseline. The median percent reductions over placebo for the FDA ITT population were: 600 mg/day 10% (16) and 12% (17); 900 mg/day 16 (16) and 24% (17), and 1200 mg/day 22% (17) and 27% (18). In pairwise comparisons, the 600 mg dose was not statistically better than placebo but the 900 mg (16,17) and 1200 mg (16,18) doses were ($p < .001$).

The results of maintenance-phase data for patients reaching their target dose were superior, as expected, to the ITT populations: the median percent reduction in seizure number

over the baseline number for the 600 mg/day dose was 20% (16); for the 900 mg/day dose the reduction was 26% better than placebo (17), and for the 1200 mg/day dose 37% (18). Seizure-free rates counted from the time of randomization were low, as expected in a refractory population: 3.2% at 600 mg/day and 4.7% at 900 mg/day, not statistically different from the 1.2% placebo rate (17).

The best results were from the third trial, which enrolled 306 patients, mostly from the US, randomized to only one dose of EZG, 1200 mg/day, or to placebo as adjunctive therapy (18).

Tolerability

Effectiveness is a balance between efficacy and tolerability. A good measure of tolerability is the total dropout rate, which is more objective than the dropout rate attributed to adverse effects by the investigators. Most dropouts were during the titration period. During the first randomized clinical trial, dropouts during dose titration were 25% for the 600 mg/day arm, 38% for the 900 mg/day arm, and 50% for the 1200 mg/day arm (16). Because of the high dropout rate in the 1200 mg/day cohort, doses were limited to 900 mg/day for a later study: dropouts during titration were placebo 9%, 600 mg/day 13%, and 900 mg/day 16% (17). However, when the 1200 mg dose was tried again in the third trial, the dropout rate was only 27% compared to 9% for placebo (18). When data from clinical trials with this design are published, the statement is often made that the titration was forced, with the implication that slower titrations would increase tolerability. However, this does not completely explain the differences in dropout rates between the three EZG studies. The first trial permitted a rather leisurely 8-week titration to the target dose (16), but recorded more dropouts than the second trial, which provided for only a 4-week titration (17). The forced titration period for the third trial was 6 weeks, but it had the fewest dropouts (18).

The most common reasons for dropouts attributed to adverse effects were somnolence, dizziness, and fatigue or asthenia (16,17,18). Adverse effects with a definite dose-relationship were dizziness and somnolence (17). The dizziness was not usually associated with ataxia. There were also some instances of blurred vision, confusion, dysarthria, and -unusually for an antiepileptic drug- urinary tract infection (18).

Bladder epithelium contains voltage-gated potassium channel isoforms $K_v7.2$ and 3, and EZG causes urodynamic effects in rats (19). Accordingly, most participants in clinical trials had systematic measurements of post-voiding residual volumes and were administered a standard urological questionnaire designed to detect symptoms of prostatic hypertrophy (20). Among 1365 patients from 7 clinical trials, symptoms related to voiding difficulty or urinary retention occurred in 8.6%, slight increases in post-voiding residual volumes were recorded in 3.0%, and 5 of these 1365 patients required urinary catheterization (21). Symptoms resolved when EZG was discontinued. EZG can cause a reddish or orange discoloration of the urine, which is harmless and unrelated to bladder function.

Safety

So far, EZG therapy appears relatively safe. Concerns about possible cardiac effects of potassium-channel actions have



been allayed by the normal results of ECGs in human trials, including a 24-hour Holter monitor in the first trial (16). In contrast to some other antiepileptic drugs, EZG-treated subjects were virtually rash-free (16,17,18), had no visual field effects with formal testing (16), and had no clinically significant changes in hepatic enzymes or hematological parameters (16,17,18). In clinical trials, there were single reported cases of suicidal ideation and of psychosis (16). Sudden death rates did not exceed reported rates for individuals with refractory epilepsy (16,17,18).

Comparative Efficacy

For a new antiepileptic drug to keep marching toward commercialization, there seems to be a magic number for median percent seizure reduction in add-on trials of at least 30%, or at least 20% above the placebo rate. This standard, though nowhere publically endorsed and with no particular scientific merit, has remained remarkably constant for the past 20 years. This is despite protests that it may be getting harder and harder to obtain this result because of the availability of more and more drugs. Fortunately for EZG's development program, it cleared the bar. It is debatable whether results from adjunctive trials in such populations ought to be used in meta-analyses of comparative drug effectiveness. Results from EZG trials are not dissimilar to those from trials of other new drugs for refractory epilepsy (22). Also unknown is how these numbers will translate into clinical usefulness; apparent potency in trials does not necessarily predict wide clinical use. Is EZG a more efficacious drug than others? We cannot say until direct comparative trials are done.

Practical Use

Regulatory labeling is incomplete. Clinical trials enrolled men and women between the ages of 16 and 75 (16,17,18). In Europe, EZG labeling will likely reflect approval for patients 18 years and older (1). The best target dose for most patients in terms of balancing efficacy and tolerability appears to be about 900 mg/day, though 1200 mg/day is tolerated by many patients. The current formulation will require three daily divided doses.

Patients should be told of the common CNS side effects of somnolence, dizziness, and fatigue. If peak-dose dizziness occurs, taking EZG with food may help. Patients certainly should be informed that urinary discoloration may occur. Although this effect appears to be harmless, if a patient reports this it may be useful to do a urinalysis to be sure the discoloration is not caused by something unrelated to EZG therapy, such as blood.

Urinary hesitation may occur, and patients should be told this as well. A relative contraindication to EZG use may be prostatism or other pre-existing voiding difficulty. Formal screening and followup with the American Urological Association questionnaire (20) (AUA-SI) may be worthwhile in that circumstance, but is probably unnecessary in most patients. In the absence of evidence of cardiac effects, and with a good biological explanation of why EZG should not affect cardiac function (9), electrocardiographic surveillance should not be required.

Place in therapy

It is to be expected that EZG will be tried for patients with refractory partial-onset seizures who have failed other drugs. Most of the interest in this drug derives from its unique mechanism of action. It is tempting to say that we ought to try it in patients who have failed drugs with other mechanisms, but that hardly narrows the field of potential candidates. Will EZG be a path toward rational polytherapy of epilepsy? Theoretically, it should be complementary to both sodium-channel blocking drugs or GABA-facilitating drugs. A critical question is whether EZG displays synergism with other drugs, or merely an additive effect. Clues from animal isobolographic work suggest synergism with some drugs (23) but human evidence of antiepileptic synergy has not been easy to obtain even for older drug combinations. It is reasonable to consider possible additive side effects, such as dizziness or somnolence, when selecting drug combinations.

Besides rational polytherapy, another holy grail of epileptology is the idea of matching drugs to correct specific pathologies. A genetic abnormality coding for $K_v7.2$ channels is now known to be the cause of benign familial neonatal convulsions—"third day seizures" (24). Other K_v7 channelopathies may lead to other generalized epilepsies (25,26,27). There is insufficient experience to know whether EZG has a place in the therapy of these specific syndromes. Having a silver bullet is appealing, but practically what we need more is another "broad-spectrum" antiepileptic drug. EZG holds some promise for having a broad spectrum of activity based on animal data, but it has not been tested for generalized-onset seizures. EZG may also prove useful for conditions other than epilepsy, because its target channels are ubiquitous in the nervous system.

Conclusion

Ezogabine is the first antiepileptic drug with a very specific effect on central nervous system potassium channels. It changes the angle of a critical hinge in two isoforms of voltage-gated potassium channels, facilitating the open state of the channels. Thus it opens a new avenue for therapy of refractory epilepsies. It is also a tool to sort out which syndromes are modifiable by this mechanism. It has advantages of minimal drug interactions and mostly renal excretion. There are few safety concerns and most side effects are those typically seen with antiepileptic agents. The exception is urinary retention, which may rule out its use in populations susceptible to this problem.

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