Brief Report

The Effects of Ethanol on the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Ezogabine (Retigabine)

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ABSTRACT

Background: The antiepileptic drug ezogabine (EZG; US adopted name for retigabine [the international nonproprietary name]) reduces neuronal excitability by enhancing potassium channel activity. EZG has been approved as adjunctive treatment for adults with partial-onset seizures.

Objective: The goal of this study was to examine the impact of coadministration of ethanol 1 g/kg on the safety and tolerability of EZG and the consequences of coadministration on pharmacokinetic (PK) and pharmacodynamic (PD) parameters in healthy volunteers.

Methods: In a randomized, 4-way crossover, partially double-blind study, volunteers received 4 oral treatments (EZG 200 mg + ethanol placebo [light apple juice]; placebo + ethanol 1 g/kg; EZG 200 mg + ethanol 1 g/kg; or placebo + ethanol placebo) separated by 5 to 21 days.

Results: PK and PD parameters were evaluated in 17 healthy volunteers (19 to 55 years) who were currently moderate alcohol drinkers. Ethanol coadministration increased EZG $AUC_{0-\infty}$ and C_{max} by 36% and 23%, respectively. EZG had no impact on ethanol PK. Ethanol alone impaired balance, blurred vision, and increased intoxication and dizziness. Objective tests (reaction times, response accuracy, attention, and manual tracking) were also impaired by ethanol. EZG treatment alone had no impact on PD measures other than a variable, transient increase in blurred vision (vision clear–crisp visual analog scale scores). Treatments were generally tolerated, with no serious adverse events or discontinuations owing to adverse events.

Conclusions: Ethanol increased EZG exposure, which did not seem to be clinically relevant. Except for an increase in blurred vision, impairment effects observed were related primarily to ethanol and were not exacerbated by the addition of EZG, which was generally tolerated with or without ethanol. (*Clin Ther*. 2013;35:87–93) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: ethanol, ezogabine, pharmacokinetics, retigabine, safety.

INTRODUCTION

Ezogabine (EZG; US adopted name for retigabine, the international nonproprietary name for *N*-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester) is an antiepileptic drug (AED) that enhances the activity of neuronal, voltage-gated KCNQ (Kv7) potassium channels, thereby reducing neuronal excitability.[1–6] EZG has been shown to be effective and generally tolerated as an adjunctive therapy in adults with partial-onset seizures[7–9] and has been approved by regulatory authorities, including those in the United States and the European Union.

Because alcohol is consumed in many societies, it is important to understand its potential pharmacokinetic (PK) and pharmacodynamic (PD) interactions with any drugs that may be administered long term, such as AEDs. Alcohol intake in moderate amounts (1–2 drinks per day) does not usually increase seizure frequency or affect the PK of AEDs; however, patients who abuse alcohol are at increased risk of seizures.[10] In addition to ethanol's recognized cognitive and executive function effects, it is well known that it can affect plasma concentrations of some AEDs, such as phenytoin and carbamazepine, and warnings about such ef-

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fects feature in the information supplied to prescribers and patients.[11]

EZG is rapidly absorbed after oral administration, has linear PK, reaches C_{max} within 1.5 hours, and has a mean terminal $t_{½}$ of 6 to 8 hours.[12] EZG is metabolized extensively through formation of an *N*-acetyl metabolite (NAMR) and glucuronidation of both EZG and NAMR.[13,14] The excretion of EZG and its metabolites occurs predominantly through the renal route, with 84% of the orally administered dose recovered in the urine.[14] In vitro, in vivo, and Phase III clinical studies have shown that the drug-interaction potential of EZG is low.[7–9,13,14]

In the current study, the effects of coadministration of an intoxicating dose of ethanol on the PK, PD, safety, and tolerability of EZG were studied, as were the effects of EZG on the PK and PD of ethanol.

METHODS

Healthy adults aged 19 to 55 years (minimum weight, 50 kg; body mass index, 18–33 kg/m^2), who were current moderate alcohol drinkers, were eligible for inclusion. Moderate alcohol use was defined as consuming 7 to 28 drinks per week with ≥5 standard drinks (1.5 US fl oz [44 mL] of hard liquor [spirits], 5 fl oz [148 mL] of wine, or 12 fl oz [355 mL] of beer) consumed in the past month on at least 1 occasion.

Study Design

A partially double-blind, randomized, 4-way crossover study (study identifier: VRX-RET-E22–107) was performed outside the United States to investigate PK and PD interactions between a single dose of EZG 200 mg and an intoxicating dose of ethanol (1 g/kg). The study was not fully double-blind because the taste and odor of ethanol are difficult to mask. The safety and tolerability of the EZG and ethanol combination were also assessed.

The study consisted of 3 periods: screening/qualifying, treatment, and posttreatment follow-up. The screening and qualifying period lasted up to 56 days. During the qualifying period, volunteers were evaluated for their ethanol tolerance as demonstrated by a blood ethanol concentration of at least 0.06% (0.06 g of ethanol/100 mL [13.03 mmol/L]) and characteristic PD response after a 1-g/kg ethanol dose. In volunteers who were eligible for inclusion, screening evaluations included physical examination, medical history, review and assessment of AEs and concomitant medications, 12-lead ECG, and clinical laboratory tests.

The treatment period consisted of four 2-night inpatient treatment sessions. The washout period between treatments was 5 to 21 days, which was considered sufficient to ensure an adequate washout of EZG and absence of carryover effects. The posttreatment follow-up consisted of safety assessments and was conducted 3 to 14 days after the last treatment or at the time of premature withdrawal.

Eligible volunteers who had provided informed consent were randomized to 1 of 4 study sequences and received the following treatments in the order specified by the study sequence: EZG alone (EZG 200 mg plus ethanol placebo [light apple juice]), ethanol alone (EZG placebo plus 1 g/kg of ethanol beverage), EZG plus ethanol (EZG 200 mg plus 1 g/kg of ethanol beverage), and placebo (EZG placebo plus ethanol placebo). Ethanol and ethanol placebo were consumed within 20 minutes after a dose of EZG or EZG placebo.

Assessments

Blood samples were collected at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dosing for EZG and EZG placebo, and at predose and 0.5, 1, 1.5, 2, 4, 8, and 12 hours after dosing for ethanol and ethanol placebo. LC-MS was used for quantitative bioanalysis of EZG (based on Knebel et al[15]), and gas chromatography–flame ionization was used for quantitative bioanalysis of ethanol.

The following PK parameters were determined by using noncompartmental methods for EZG and ethanol: C_{max}, T_{max}, AUC from time zero to the last quantifiable concentration ($AUC_{0-\tau}$), and $AUC_{0-\infty}$.

PD assessments were conducted at predose and ~0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose during the qualifying period and at ~1 hour predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose during the treatment period. PD assessments included subjective effects on visual analog scales (VAS) for dizziness, feeling sick, nausea, intoxication, attention span, and vision, and objective tests including the balance platform (AMTI AccuSway Plus Balance Platform [AMTI, Watertown, Massachusetts]) for body sway and postural stability; the choice reaction time test for total reaction, recognition reaction, and motor reaction times; and the divided attention test (computer simulation) for manual tracking and target detection.

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