Vigabatrin Lacks Proarrhythmic Potential: Results from a Thorough QT/QTc Study in Healthy Volunteers

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ABSTRACT

Purpose: A thorough QT study was performed to assess the proarrhythmic potential of vigabatrin, an antiepileptic drug approved in the United States for the treatment of infantile spasms and refractory complex partial seizures.

Methods: In this Phase I, randomized, double-blind, placebo- and active-controlled (moxifloxacin), 4-sequence, crossover study conducted at a single center, healthy participants received 1 of 4 randomly assigned treatments: 3.0 g vigabatrin solution (therapeutic dose) and 1 moxifloxacin placebo tablet; 6.0 g vigabatrin solution (supratherapeutic dose) and 1 moxifloxacin placebo tablet; 400 mg moxifloxacin and vigabatrin placebo solution; moxifloxacin placebo tablet and vigabatrin placebo solution.

Findings: Mean changes from baseline in placebo-corrected QTcF, QTcB, and QTcI with vigabatrin 3.0 g and 6.0 g indicated no signal for any QTc effect relative to baseline. All 1-sided upper 95% confidence intervals for the differences between each vigabatrin dose and placebo were <10 ms at all time points. QTcF was unaffected by increasing plasma vigabatrin concentrations; no arrhythmias were observed in any treatment group. Low rates of first-degree atrioventricular block, sinus tachycardia, and sinus bradycardia occurred in all treatment groups. Most adverse events were mild.

Implications: The findings from this thorough QT study are consistent with existing clinical data and confirm a lack of proarrhythmic potential of vigabatrin. (*Clin Ther*. 2017;39:1639–1648) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: ECG, infantile spasms, QT interval, refractory complex partial seizures, thorough QT, vigabatrin.

INTRODUCTION

Vigabatrin is a selective γ-aminobutyric acid transaminase (GABA-T) inhibitor with antiepileptic activity approved in the United States as a monotherapy for infants aged 1 month to 2 years of age with infantile spasms and as adjunctive therapy for patients aged ≥ 10 years with refractory complex partial seizures who have responded inadequately to several alternative treatments.[1] In the European Union, vigabatrin is indicated for use as adjunctive therapy for refractory complex partial seizures in adults and children and as first-line therapy for infantile spasms.[2]

Some noncardiovascular drugs including AEDs have been shown to delay ventricular repolarization, which can lead to fatal arrhythmias such as torsades de pointes.[3] While the risk for noncardiovascular drugs to induce fatal arrhythmias is generally low, some drugs can prolong the QT interval via the same mechanism as proarrhythmic drugs, namely blockade of the potassium channel encoded by *hERG*.[4] Therefore, conducting a thorough QT (TQT) study[5] of all new molecular entities improves drug safety by ensuring that clinically relevant drug concentrations do not cause prolongation of the corrected QT (QTc) interval that exceeds the threshold needed to delay ventricular repolarization.[5,6]

Patients with epilepsy have significantly longer QT intervals than do age-matched controls,[7] and patients with uncontrolled seizures often have abnormal cardiac repolarization, which may contribute to an

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increased risk for sudden unexpected death in epilepsy.[8] Though vigabatrin has been successfully used in the clinic since the 1990s without any cardiac safety concerns, the potential for vigabatrin to affect the QT interval was evaluated in 2008 following the implementation of the International Conference on Harmonisation (ICH) E14 guideline for the clinical cardiac evaluation of nonantiarrhythmic drugs in 2005.[5] To date, no pharmacologic, preclinical, or clinical data suggest proarrhythmic properties of vigabatrin.

SUBJECTS AND METHODS

Ethical Conduct and Regulatory Review

This Phase I TQT study was conducted at a single site (SeaView Research, Miami, Florida) between April 2008 and May 2008 in accordance with the protocol and Good Clinical Practice as provided in the US Food and Drug Administration Code of Federal Regulations governing clinical study conduct and the ICH Good Clinical Practice that meet the principles founded in the Declaration of Helsinki. Protocol approvals were obtained in writing from the institutional review board (Independent Investigational Review Board Inc, Plantation, Florida). All participants provided written informed consent in compliance with Title 21 of the Code of Federal Regulations Part 50 before entering the study and before any procedures were performed. The investigator was responsible for ensuring that all consent forms and/or Health Insurance Portability and Accountability Act authorization were submitted to the institutional review board for approval.

Study Design and Procedure

In this Phase I, randomized, double-blind, placebo- and active-controlled (moxifloxacin), single-center, 4-sequence, crossover study, healthy participants were confined to the clinic throughout the 12-day study duration. Each participant was assigned to receive the following treatments in 1 of 4 randomly assigned sequences: 3.0 g vigabatrin solution (therapeutic dose) and 1 moxifloxacin placebo tablet; 6.0 g vigabatrin solution (supratherapeutic dose) and 1 moxifloxacin placebo tablet; 400 mg moxifloxacin and vigabatrin placebo solution; moxifloxacin placebo tablet and vigabatrin placebo solution. Dosing occurred in the morning on days 1, 4, 7, and 10, followed by a 2-day washout period prior to the next randomized treatment period (Figure 1). All study drugs were orally administered after an overnight fast. Moxifloxacin 400 mg was included as a positive control to establish assay sensitivity. With the exception of a study statistician, the sponsor, investigative site, clinical unit personnel, and participants remained blinded to the treatment assignment throughout the course of the study.

For the QTc evaluations, three ECGs from a Holter recorder were collected 2 minutes apart at baseline (day –1) and on days 1, 4, 7, and 10 before dosing (–1.5, –1.0, –0.5, and 0 hours) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, and 22 hours after dosing (Figure 1). All ECGs from a Holter recorder were read in a blinded manner by a cardiologist at a central laboratory (Cardiocore, presently BioTelemetry Inc, Rockville, Maryland) for both interval measurements and overall interpretation. To ensure participant safety, standard 12-lead ECGs were performed at screening, day –2, day 12, and at the following time points on days 1, 4, 7, and 10: before dosing (0 hour) and 0.75, 8, and 24 hours after dosing. All standard 12-lead ECGs were collected using a standard ECG machine after the participant had been resting in a supine position for at least 10 minutes. ECGs were interpreted as normal, abnormal not clinically significant, or abnormal clinically significant.

Vital signs were measured ~20 minutes before the collection of any blood samples for pharmacokinetic (PK) assessment. Blood samples were collected at the following time points on days 1, 4, 7, and 10: before dosing (0 hour) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, 23, 36, and 48 hours after dosing; ~60 samples per subject (180 mL of blood) were collected from each participant for analysis of plasma vigabatrin and moxifloxacin concentrations. Clinical laboratory profiles were obtained at screening, day –2, and day 12 (end of study) or early withdrawal. Blood samples for the analysis of serum chemistry and hematology, as well as urine specimens for urinalysis, were sent to a central laboratory (Covance Bioanalytical Services LLC) for analysis and reporting. Plasma concentrations of vigabatrin and moxifloxacin were assayed with respect to analyte using a validated LC-MS/MS. The lower limits of quantification in plasma were 0.200 μg/mL for vigabatrin and 25 ng/mL for moxifloxacin.

All patients with any adverse event (AE) that occurred during the study were followed up until the