Received: 11 January 2022 | Revised: 26 April 2022 | Accepted: 2 May 2022

DOI: 10.1111/cts.13311

ARTICLE

Cardiac sodium channel inhibition by lamotrigine: In vitro characterization and clinical implications

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Funding information
GSK funded this study

Abstract

Lamotrigine, approved for use as an antiseizure medication as well as the treatment of bipolar disorder, inhibits sodium channels in the brain to reduce repetitive neuronal firing and pathological release of glutamate. The shared homology of sodium channels and lack of selectivity associated with channel blocking agents can cause slowing of cardiac conduction and increased proarrhythmic potential. The Vaughan-Williams classification system differentiates sodium channel blockers using biophysical properties of binding. As such, Class Ib inhibitors, including mexiletine, do not slow cardiac conduction as measured by the electrocardiogram, at therapeutically relevant exposure. Our goal was to characterize the biophysical properties of $Na_V1.5$ block and to support the observed clinical safety of lamotrigine. We used HEK-293 cells stably expressing the $hNa_V1.5$ channel and voltage clamp electrophysiology to quantify the potency (half-maximal inhibitory concentration) against peak and late channel current, on-/off-rate binding kinetics, voltage-dependence, and tonic block of the cardiac sodium channel by lamotrigine; and compared to clinically relevant Class Ia (quinidine), Ib (mexiletine), and Ic (flecainide) inhibitors. Lamotrigine blocked peak and late $Na_V1.5$ current at therapeutically relevant exposure, with rapid kinetics and biophysical properties similar to the class Ib inhibitor mexiletine. However, no clinically meaningful prolongation in QRS or PR interval was observed in healthy subjects in a new analysis of a previously reported thorough QT clinical trial (SCA104648). In conclusion, the weak $Na_V1.5$ block and rapid kinetics do not translate into clinically relevant conduction slowing at therapeutic exposure and support the clinical safety of lamotrigine in patients suffering from epilepsy and bipolar disorder.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Lamotrigine allows for control of epileptic seizures by decreasing central nervous excitability, a property dependent on neuronal sodium channels.

WHAT QUESTION DID THIS STUDY ADDRESS?

Our study attempted to explore the implications of $Na_V1.5$ sodium channel blocking properties of lamotrigine on cardiac conduction in healthy subjects at therapeutic doses.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Lamotrigine inhibits $Na_V1.5$ at therapeutic exposure with rapid kinetics and biophysical properties similar to mexiletine, a class Ib molecule. These findings support the observed clinical safety of lamotrigine in patients suffering from epilepsy and bipolar disorder.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Although there is agreement that class Ib-like agents may carry risks for proarrhythmia, particularly in higher risk subpopulations with underlying cardiac disease, heart failure, and advanced conduction disorders; our results suggest that the $Na_V1.5$ sodium channel blocking properties of lamotrigine at therapeutic doses are not associated with electrocardiogram changes of clinical concern for the overall population.

INTRODUCTION

Lamotrigine was first approved as an antiseizure medication (ASM) in the 1990s, and subsequently as maintenance treatment for bipolar disorder. Recognized by the World Health Organization on the "Essential Medicines List"; lamotrigine is approved for use in over 100 countries worldwide. Lamotrigine, along with other ASMs, reduces epileptiform activity and allows for control of tonic–clonic seizures by decreasing central nervous excitability, a property driven by neuronal sodium channels.[1]

Sodium channel blockers have been the cornerstone for managing epilepsy, and neuronal sodium channels are the target for many first-, second-, and third-generation antiseizure agents.[2] As such, lamotrigine produces a block of sustained repetitive firing in neurons and inhibits pathological release of glutamate; as well as inhibiting glutamate-evoked bursts of action potentials.[3–7] Within the sodium channel, lamotrigine binds to a local anesthetic site, which is conserved across channel isoforms.[8]

Of the voltage-gated sodium channels ($hNa_V1.1$–1.9), $hNa_V1.5$ ($Na_V1.5$) is predominately expressed in the heart and is responsible for the rapid depolarization of the cardiac action potential.[9] Depending on the degree and duration of, sodium channel blockade may slow myocardial conduction resulting in prolongation of the QRS complex and/or PR-interval of the electrocardiogram (ECG)—the basis for both antiarrhythmic and proarrhythmic activity. Prolongation of either may indicate the risk for arrhythmia, particularly in subpopulations with underlying functional or structural cardiac disease, and advanced conduction disorders where cardiac sodium channel density is reduced.[10–13]

Many drug classes, including ASMs, have been associated with cardiac conduction and rhythm abnormalities.[14,15] Sodium channel blockers may cause arrhythmias, particularly at high dosage,[11] including unmasking of an underlying disease, such as Brugada Syndrome (BRS).[16] Because BRS is often caused by loss-of-function $Na_V1.5$ mutations, potent channel blockers, including flecainide and ajmaline, are often used clinically to unmask the underlying phenotype and to evaluate severity of disease.[16]

The Vaughan-Williams classification categorizes drugs for cardiac or other indications as class I antiarrhythmics producing moderate (Ia), weak (Ib), or marked (Ic) $Na_V1.5$ blockade.[17] These subclassifications arose from biophysical properties—specifically, kinetics of drug-channel binding. In the Cardiac Arrhythmia Suppression Trial (CAST), patients receiving class Ic agents flecainide or encainide displayed significantly increased incidence of arrhythmic death when compared to placebo.[18,19] Of the three categories, these drugs exhibit the slowest on-/off-set binding kinetics. Class Ib exemplars, such as mexiletine, have always been considered less risky with respect to cardiac liability; primarily because of their rapid dissociation from $Na_V1.5$.[20,21] Importantly, class Ib agents were never studied in the CAST trials and have been prescribed safely for quite some time. For example, phenytoin (ASM)

has been proven safe in patients dosed at efficacious exposures since the 1930s; except in those with marked cardiac comorbidities.[22] Additionally, whereas both disopyramide (Ia) and flecainide (Ic) caused ST elevation and QRS prolongation in patients with BRS, mexiletine (Ib) showed no deleterious effects.[23]

The present study was designed to determine the $Na_V1.5$ sodium channel blocking properties of lamotrigine relative to class I anti-arrhythmic drugs and to explore the potential implications for cardiac effects at therapeutically relevant concentrations. In addition, we summarize clinical pharmacology data from historical human trials to support the clinical cardiac safety of lamotrigine at the currently approved dose range.[24,25]

METHODS

An outline of the experimental protocols used in the current investigation and evaluation of potential clinical implications is depicted in Figure 1. Nonclinical protocols can be found below. Clinical data generated in healthy subjects (Appendix S1) from a previously published thorough QT/QTc study (TQT; (SCA104648)) were used in a post hoc analysis to evaluate how in vitro data correlates with ECG measures at therapeutically relevant exposure.[24,25]

$Na_V1.5$ manual patch clamp electrophysiology

Drug and solution preparation

Lamotrigine (internal), flecainide (Sigma F6777-100MG), mexiletine (Sigma M2727-100G), quinidine (Sigma Q0750-5G), and ranolazine (Cayman 15604) were prepared in 100% DMSO. ATXII (Alomone) was prepared in deionized H_2O. Tetrodotoxin (TTX:Enzo) was resuspended in DMSO at 10 mM and used as a suspension. Compound stock solutions (or suspension for TTX) were then diluted to working concentrations in an external recording buffer (contained in mM: 35 NaCl, 4 KCl, 10 HEPES, 10 glucose, 2 $CaCl_2$, 1 $MgCl_2$, and 105 NMDG [0.22 µm filtered, pH 7.35, 315 mOsm]). The final concentration of DMSO in the external buffer was ≤0.3%. The $Na_V1.5$ internal recording solution contained (in mM): 110 CsF, 20 CsCl, 10 HEPES, 10 EGTA, and 10 NaF (0.22 µm filtered, pH 7.35, 309 mOsm).

Cell preparation

A human embryonic kidney (HEK293) cell line stably expressing the human $Na_V1.5$ sodium channel was used to determine the effects of lamotrigine, flecainide,

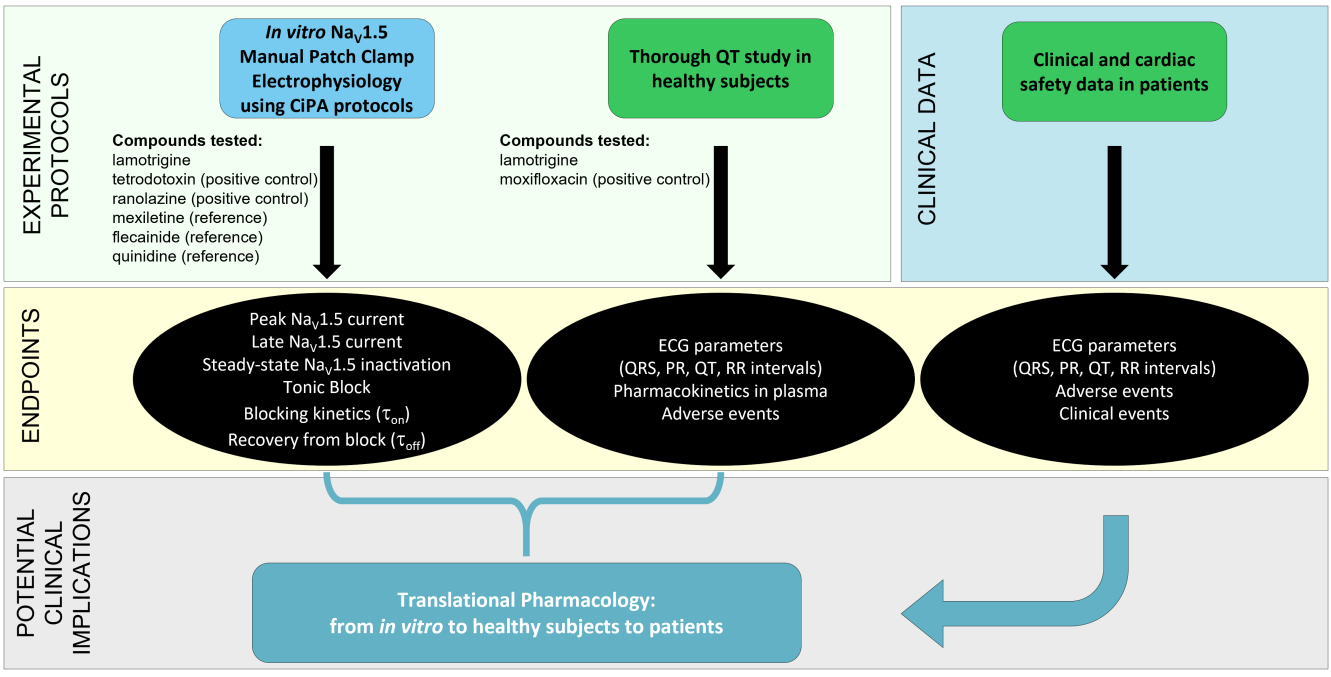

FIGURE 1 Outline of the experimental protocols and end points included in the current data analysis. Different reference compounds and positive controls were used to ensure accurate interpretation of the results. The results from in vitro electrophysiology experiments were evaluated in conjunction with data arising from healthy subjects in a thorough QT study. Last, clinical data on cardiac and cardiovascular safety were retrieved from internal and external databases. CiPA, Comprehensive In Vitro Proarrhythmia Assay; ECG, electrocardiogram.

mexiletine, quinidine, ranolazine, ATXII, and TTX on current amplitude. Cell culture media consisted of D-MEM/F12 with 15 mM HEPES buffer and L-glutamine, supplemented with 0.1 mM non-essential amino acids, 10% fetal bovine serum, 1000 units/L penicillin, 1000 µg/L streptomycin, and 400 mg/L G418 (Invitrogen) to allow for selection of $Na_V1.5$-expressing cells.

Peak $Na_V1.5$ current recording

Whole-cell manual patch clamp was performed to generate concentration-response curves using a Multiclamp 700A amplifier, Digidata 1440A digitizer, and pClamp version 10.7 data acquisition software (Axon Instruments/Molecular Devices). Recording was done at 0.1 Hz using the Comprehensive In Vitro Proarrhythmia Assay (CiPA) voltage protocol, shown inset in Figure 2b. Peak $Na_V1.5$ current amplitude was measured at the −15 mV depolarizing step as shown in the voltage protocol, and 900 µM quinidine was used as the positive control to inhibit any residual current. Peak amplitudes, either baseline or drug-treated, were measured once the current had stabilized for 2–3 min and was deemed to be at steady-state. Alternatively, if the current had not quite leveled off, but had reached a state where the current decay matched the rundown inherent in the cell during the control state, the block was deemed to be in steady-state.

Late $Na_V1.5$ current recording

Late $Na_V1.5$ current was studied using the CiPA voltage protocol in Figure 2b at a frequency of 0.1 Hz. 150 nM ATX was applied to induce late $Na_V1.5$ current, and 300 µM ranolazine was the positive control. Late current was measured at two places—as the mean inward current at the end of the −15 mV step and as the peak inward current during the ramp down phase.

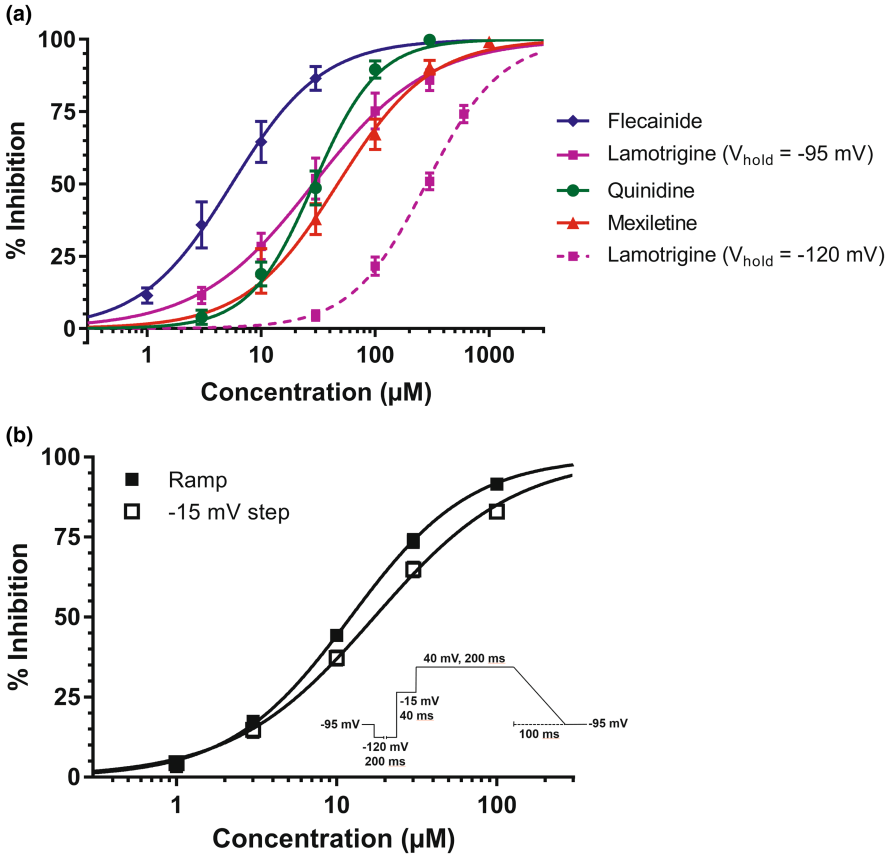

FIGURE 2 IC_{50} values for block of peak and late $Na_V1.5$ currents stably expressed in HEK293 cells. IC_{50} values are mean ± SEM. (a) Flecainide-, lamotrigine-, quinidine-, and mexiletine-mediated block of peak $Na_V1.5$ current. IC_{50} values were 47.0 ± 5.4 µM ($n = 7$), 28.9 ± 2.2 µM ($n = 4$), and 5.5 ± 0.8 µM ($n = 4$) for mexiletine, quinidine, and flecainide, respectively. IC_{50} values for lamotrigine were 280.2 ± 15.5 µM (71.8 ± 4.0 µg/ml, $n = 4$) and 28.8 ± 4.0 µM (7.4 ± 1.0 µg/ml, $n = 5$) at $V_{hold} = -120$ mV and $V_{hold} = -95$ mV, respectively. (b) Lamotrigine-mediated block of late $Na_V1.5$. IC_{50} values were 12.2 ± 0.5 µM (3.1 ± 0.13 µg/ml, $n = 4$) and 17.2 ± 0.9 µM (4.4 ± 0.23 µg/ml, $n = 4$) for the ramp and −15 mV epochs, respectively. Voltage clamp protocol in inset. IC_{50}, half-maximal inhibitory concentration.

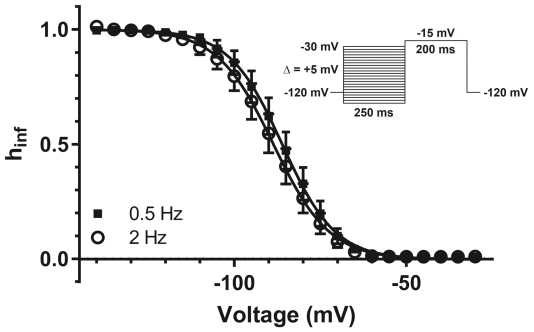

FIGURE 3 $Na_V1.5$ steady-state inactivation (h_{inf}) curves with external buffer. $V_{1/2}$ values are −86.2 ± 2.7 mV and −88.7 ± 2.8 mV at 0.5 and 2 Hz, respectively. Values are mean ± SEM. $n = 6$. Voltage clamp protocol in inset.

Steady-state inactivation of $Na_V1.5$ channels

Steady-state inactivation protocols were run at both 0.5 and 2 Hz (see inset in Figure 3). Measurements were taken as the peak inward current at V_{test} (after leak subtraction), plotted against the inactivating voltage.

Tonic and kinetic block of $Na_V1.5$

Tonic (closed state) block and blocking kinetics (τ_{on} and τ_{off}) of test articles were determined to identify the Vaughan-Williams classification of lamotrigine in comparison to known class Ia/b/c anti-arrhythmics. See Figure S1 for details.

In vitro data analysis

The data were analyzed using Clampfit 10.7 (Molecular Devices, LLC) to find the mean or peak inward current. Rundown correction and leak subtraction were performed. All fits were performed using GraphPad Prism 7 (GraphPad Software). Concentration-response curves for ion channel studies were fit to the Hill equation: $Y = Y_{max} + (([Y_{min}\text{-}Y_{max}]*IC_{50}{}^{nH})/(X^{nH} + IC_{50}{}^{nH}))$. The τ_{on} values were calculated by normalizing the data so that the first trace equaled one and using a two-phase exponential decay with the Y0 value fixed at one. The τ_{off} values were determined by fitting with either a one-phase (flecainide and 280 μM [71.7 μg/ml] lamotrigine) or two-phase (mexiletine, quinidine, and 25 μM [6.40 μg/ml] lamotrigine) exponential association. The best fits for the data were determined by AICc comparison. Significant outliers were determined by the Grubb's test (https://www.graphpad.com/quickcalcs/grubbs1/) and those cells were excluded from final analysis. Data are presented as mean ± SEM.

RESULTS

$Na_V1.5$ manual patch clamp electrophysiology

Peak $Na_V1.5$ current using CiPA voltage protocols

Concentration-response curves for peak $Na_V1.5$ current (Figure 2a) were generated for mexiletine, quinidine, flecainide, and lamotrigine at $V_{hold} = -95$ mV. The observed half-maximal inhibitory concentration (IC_{50}) concentrations were approximated for use in blocking kinetics protocols. However, when 25 μm (6.40 μg/ml) lamotrigine was used in the kinetics protocol requiring $V_{hold} = -120$ mV, it blocked only 25.5 ± 1.5% of the current (Figure 4b). A second concentration-response experiment was conducted for lamotrigine at $V_{hold} = -120$ mV and this IC_{50} concentration was used for subsequent studies.

Late $Na_V1.5$ current

Pharmacology against late sodium current was tested at two steps in the voltage protocol (Figure 2b inset). The peak inward current was measured during the ramp phase, and the mean inward current was measured between 299 and 300 milliseconds (ms) during the −15 mV depolarization (Figure 2b). Currents measured during the ramp were normalized to ranolazine (300 μM positive control). Currents measured during the −15 mV step were not normalized to ranolazine because amplitude did not return to baseline by the end of the 40 ms depolarization.

The 30 μM TTX was tested in a subset of cells individually and inhibited peak sodium current by 93.0 ± 2.0% ($n = 4$). Late current during the ramp and −15 mV epoch was inhibited at 104.7 ± 2.4% ($n = 4$) and 98.7 ± 1.1% ($n = 4$), respectively. Endogenous late sodium current was subtracted from the ATXII-induced response, suggesting that the 104.7% inhibition seen at the ramp epoch also included TTX-dependent block of endogenous current.

Steady-state inactivation properties of $Na_V1.5$

To determine the proper holding potential for measurement of recovery from block, the closed versus inactivated state properties of $Na_V1.5$ were assessed by generating a steady-state inactivation curve (Figure 3). At −95 mV, only 75.1% and 68.7% of channels were available to open at 0.5 and 2 Hz, respectively. Therefore, binding kinetics experiments were conducted at $V_{hold} = -120$ mV.

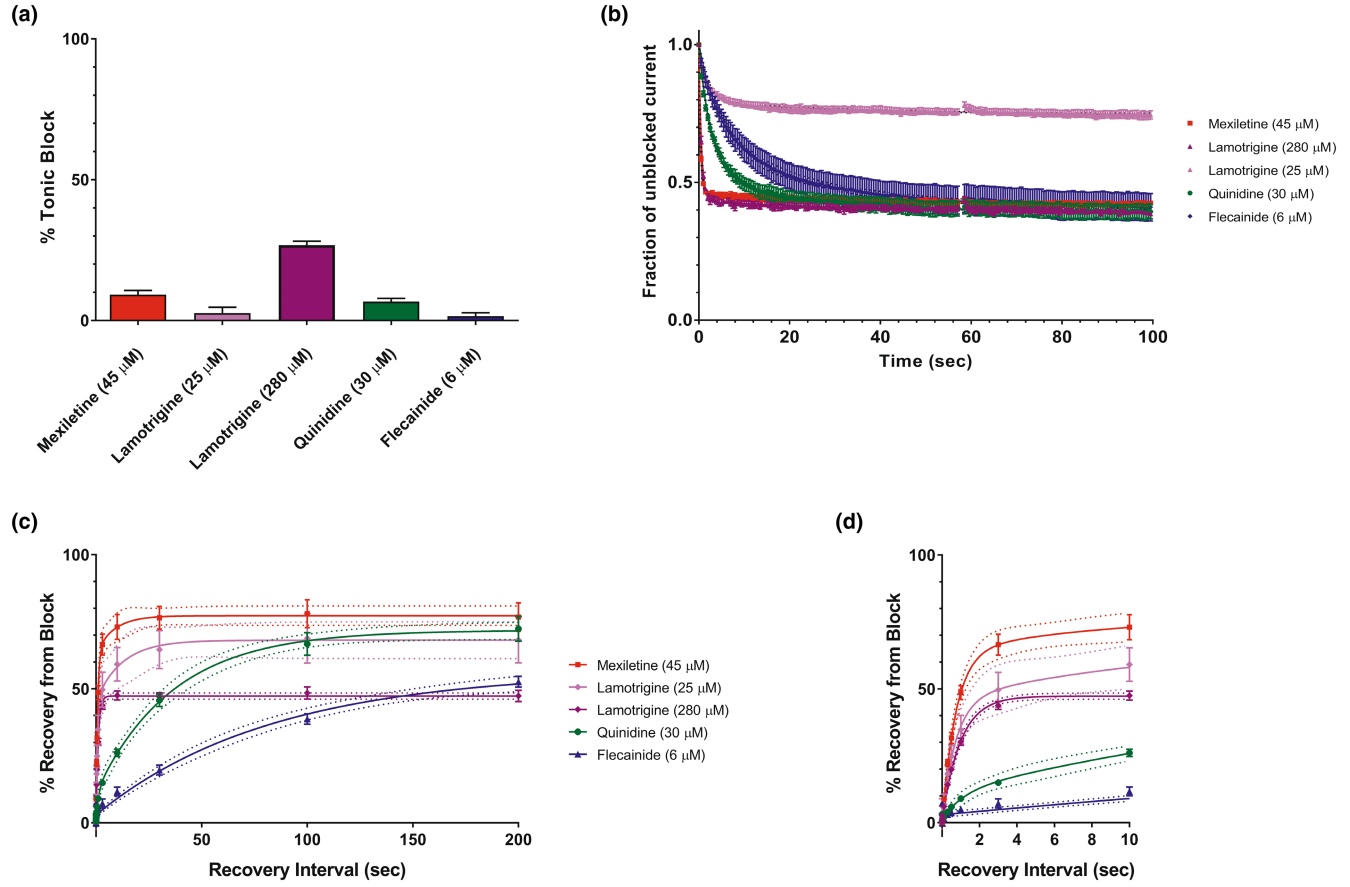

FIGURE 4 Tonic block and blocking kinetics of lamotrigine and representative class Ia, Ib, and Ic compounds. Values are mean ± SEM. (a) Tonic block of $Na_V1.5$ by mexiletine, lamotrigine, quinidine, and flecainide. Percent inhibitions are 9.2 ± 1.5 ($n = 5$), 2.6 ± 2.1 ($n = 8$), 26.8 ± 1.4 ($n = 6$), 6.7 ± 1.2 ($n = 7$), and 1.6 ± 1.2 ($n = 6$) for mexiletine, lamotrigine (25 μM), lamotrigine (280 μM), quinidine, and flecainide, respectively. (b) $Na_V1.5$ blocking kinetics (τ_{on}) of mexiletine, lamotrigine, quinidine, and flecainide (Table S2). (c) $Na_V1.5$ blocking kinetics (τ_{off}) of mexiletine, lamotrigine, quinidine, and flecainide (Table S2). The 95% confidence intervals are graphed as dotted lines. (d) Expanded view of *X*-axis (0–10 s) from panel c.

Tonic block of $Na_V1.5$

Tonic block was measured for all reference compounds and lamotrigine. Lamotrigine produced tonic block in a concentration-dependent manner (Figure 4a).

Blocking kinetics (τ_{on}) of lamotrigine

All reference compounds and lamotrigine were tested in the kinetics protocol (Figure 4) at or near respective potencies (IC_{50}). As mentioned, the potency for lamotrigine at V_{hold} of −95 mV only produced 26% block at $V_{hold} = -120$, making time constant comparisons difficult at this concentration. Mexiletine produced the smallest τ_{fast} value, and the majority of the fit (92.9%) was made up of that component. Lamotrigine (280 μM) showed a similar time course to mexiletine. Quinidine, a known class Ia anti-arrhythmic, produced intermediate kinetics with a slower τ_{fast} and a larger contribution (26.1%) by the slow component of the exponential. The class Ic anti-arrhythmic flecainide showed the slowest blocking kinetics, with the largest τ_{fast} value of the four compounds and contributions by fast and slow components of 54.9% versus 45.1%, respectively (Figure 4b and Table S1).

Recovery from block (τ_{off}) by lamotrigine

Figure 4c,d (Table S1) show the dissociation kinetics for lamotrigine and the reference compounds. Figure 4d is a magnified view of the first 10 s of Figure 4c, to further illustrate the recovery from block during the early pulse intervals. Mexiletine produced the smallest τ_{fast} value at 0.8 ± 0.03 s, and a large contribution of this recovery (83.2%) is attributable to that time constant. Both 25 and 280 μM lamotrigine behaved very similarly to mexiletine. The lower concentration of lamotrigine displayed a τ_{fast} of 0.8 ± 0.1 s that comprised 58.0% of the fit. The τ_{slow} component was 15.6 ± 5.0 s, which is 2.4-fold faster than

quinidine's slow time constant (37.7 ± 5.9 s). Lamotrigine at 280 μM was adequately fit to a single exponential with a τ = 1.0 ± 0.04 s. A notable difference between the two concentrations of lamotrigine was the amount to which the channels recovered from block after the 200-s hyperpolarization at −120 mV. The 25 μM lamotrigine allowed channels to recover by 68.2%, which was very similar to mexiletine. However, channels exposed to 280 μM lamotrigine only recovered by 47.3%, which we suggest is a consequence of the tonic block mentioned earlier. Quinidine produced an intermediate recovery, with the largest component of its fit contributed by the τ_{slow}. Flecainide was adequately fit to a single exponential and was the slowest of the controls tested.

Human cardiac conduction in healthy subjects

Data were available from 54 subjects exposed to three different doses of lamotrigine (100, 300, and 400 mg/day) and placebo, resulting in a total of 5564 time-matched PR and QRS interval and lamotrigine concentrations and 20,291 PR and QRS intervals while receiving placebo (Appendix S1 and Table S2).

The 5th to 95th percentile ranges of the maximum lamotrigine concentrations at steady-state evaluated in the TQT study were 1.8–4.0 μg/ml for a dose of 50 mg b.i.d. (100 mg/day), 4.8–10.8 μg/ml for 150 mg b.i.d. (300 mg/day), and 7.5–14.0 μg/ml for 200 mg b.i.d. (400 mg/day).

For brevity, here, we only provide figures for the linear regression of change in PR and QRS from baseline versus lamotrigine concentration (Figure 5). The linear regression results for absolute PR and QRS can be found in the Appendix S1 (Figure S2).

An increase in PR interval is observed with increasing concentrations of lamotrigine. At a concentration of 15 μg/ml, the PR interval is expected to increase by 18.15 ms, from a mean 151 ms at baseline to mean 169 ms at a lamotrigine concentration of 15 μg/ml. However, when analyzed as a change from baseline, lamotrigine could increase the PR interval up to 6.18 ms, showing the importance of baseline PR as a determinant of PR interval prolongation (Figure 5a and Figure S2A). The 95th percentile of the PR interval in the placebo data was 190 ms (or 12 ms as the change from baseline). This variation in PR interval in placebo-treated subjects indicates that changes in PR interval following the highest lamotrigine dose are within the same range.

By contrast, a decrease in QRS interval is observed with increasing concentrations of lamotrigine (Figure 5b and Figure S2B). The linear regression for change in QRS from baseline versus lamotrigine concentrations (Figure 5b) showed a statistically significant correlation (ΔQRS[%] = 0.0239 • lamotrigine concentration [μg/ml], p = 0.012). Linear regression of absolute QRS values versus lamotrigine concentrations (Figure S2B) showed that at concentrations of 15 μg/ml, the QRS interval decreases by 5.94 ms. None of the subjects had a QRS interval of >120 ms while on lamotrigine. For comparison, in subjects receiving placebo, three of 20,291 QRS observations were >120 ms, all from the same subject (1 of 145).

To ensure adequate interpretation of the data, a sensitivity analysis was performed to assess the impact of high PR baseline values on the overall results. In subjects receiving placebo, seven of 20,291 PR observations were >220 ms from three subjects (3 of 145). Exclusion of one subject from the analysis (Table S3) with a high baseline PR interval (i.e., 212 ms prior to administration of moxifloxacin and 225 ms prior to the administration of lamotrigine) resulted in a halving of the slope of PR interval increase per μg/ml of lamotrigine (from 1.21 to 0.61 ms/μg/ml; Figure S2A and Figure S3C). However, the slope in PR change from baseline per μg/ml of lamotrigine increased slightly when excluding the outlier (from 0.412 to 0.445 ms/μg/ml; Figure 5a and Figure S3A). Given the variation in baseline PR interval, inclusion of this subject has provided confidence that the results represented an unbiased and more conservative scenario for the evaluation of potential effect of lamotrigine on PR interval.

DISCUSSION

In vitro $Na_V1.5$ electrophysiology

The purpose of the current study was to assess the pharmacological effects of lamotrigine on $Na_V1.5$ currents. Biophysical characterization of the compound was performed to illustrate potency and state-dependence of channel block, kinetics of binding (τ_{on}) and dissociation (τ_{off}), with comparison to clinically relevant drugs. Further, we reviewed clinical data from a previously reported human trial to support the safety of lamotrigine.

Lamotrigine peak concentrations vary between 1.8 and 14.0 μg/ml (7.0 to 54.5 μM; or 3.15 to 24.5 μM peak unbound concentration) across the approved dose range. Lamotrigine blocked peak sodium current with an observed potency, similar to previous reports in the literature.[11,26] The 10-fold difference in potency at a depolarized potential suggests the compound exhibits voltage-dependent block of inactivated channels, as ~25–30% of channels are inactivated at this potential.

Although these in vitro patch clamp studies are contemporary, extensive nonclinical cardiac safety assessment was conducted for lamotrigine during its

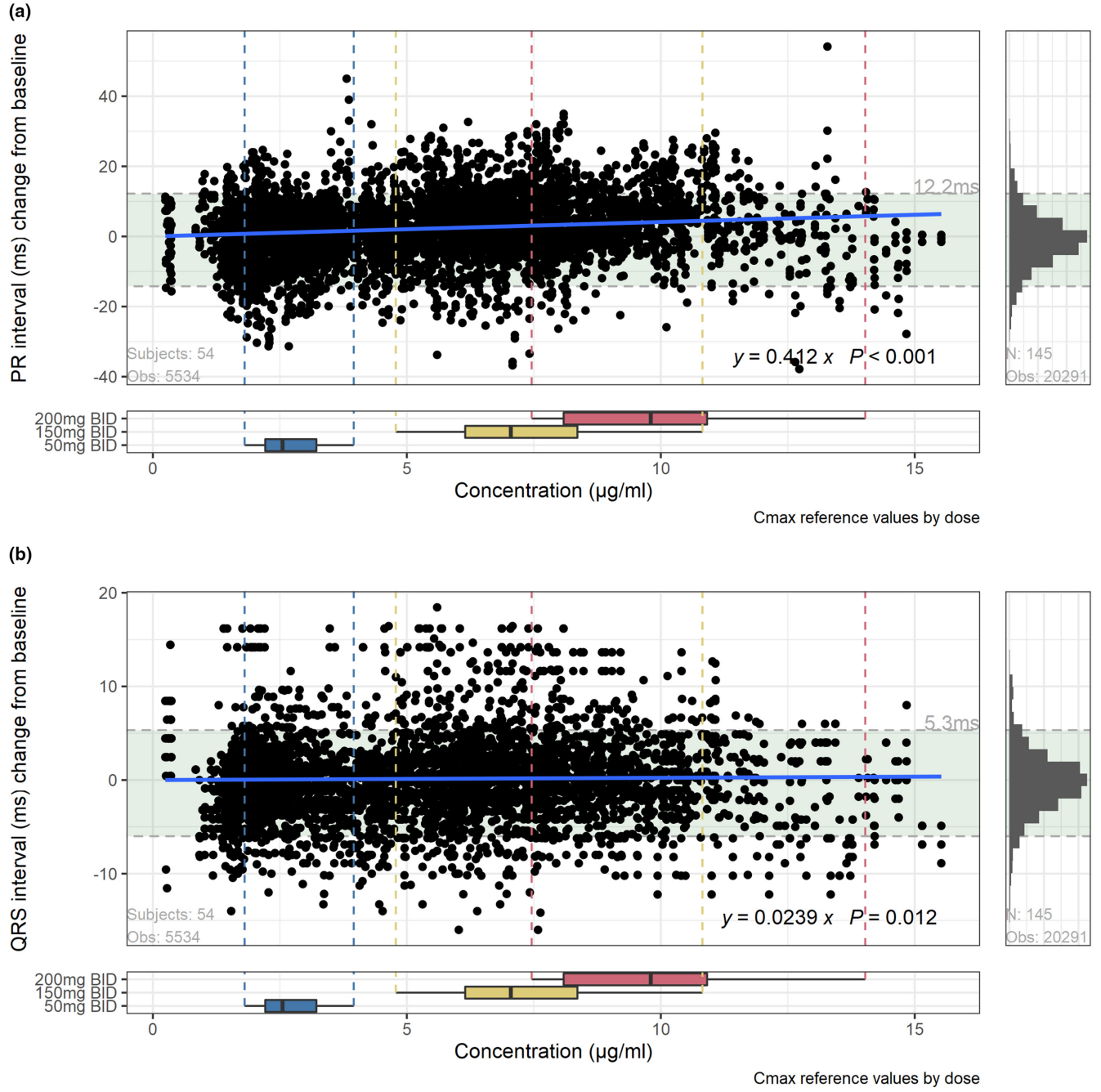

FIGURE 5 TQT study results. The green-shaded area corresponds to the 5th and 95th percentiles of the placebo group (right panel). The colored box-plots correspond to the C_{max} ranges for each dose level. The whiskers of the box-plot extend to the 5th and 95th percentiles. The blue line is a linear model fit to the data, with the estimated parameters and equation shown in the bottom right. The *p* value indicates the statistical significance of the slope value being different from zero. (a) Lamotrigine concentration versus PR as change from baseline, (b) lamotrigine concentration versus QRS interval as change from baseline. These figures were produced from a contemporary re-analysis of data previously published in Dixon et al. (2008[24] and 2011[25]), as cited, to specifically investigate and model conduction slowing at therapeutic exposure to lamotrigine in healthy subjects. C_{max}, maximum plasma concentration; TQT, thorough QT.

development in the late 1980s to early 1990s (data not reported). In canine purkinje fibers, the action potential upstroke (dV/dt) was inhibited by <10% at 30 µM, whereas a similar reduction was observed at 100 µM in isolated guinea pig myocytes. These concentrations remain 1.1- to 3.8-fold higher than the peak unbound concentration observed in humans and support a lack of translation of cardiac sodium channel block to meaningful slowing of conduction. Additionally, the potency (IC_{50}) of lamotrigine to block the hERG potassium channel, responsible for cardiac repolarization, was reported as 229 µM (58.6 µg/ml).[27]

Although lamotrigine is not approved to treat cardiac arrhythmias, we compared its kinetic properties of $Na_V1.5$ block to reference antiarrhythmic agents (class I) with established clinical safety profiles. Lamotrigine produced an on-rate of binding similar to mexiletine. The fast component of its time course was within 1.6-fold of mexiletine (class Ib) and 4.7- and 8.4-fold faster than quinidine (class Ia) and flecainide (class Ic), respectively; and the contribution by τ_{fast} was >92% for both lamotrigine and mexiletine. Lamotrigine also behaved similarly to mexiletine in recovery from block with rates 1.4-fold faster than quinidine. Additionally, the high concentration of lamotrigine produced off-rate kinetics >86-fold faster than flecainide. The binding kinetics observed for lamotrigine are comparable to those obtained for class Ib anti-arrhythmics in published reports, further supporting this classification.[21] Although class Ia and Ic drugs tend to produce channel block and slowing of conduction well below the resting heart rate in humans, the rapid kinetics of Ib-agents preclude accumulation of meaningful block until very high heart rates. Additionally, lamotrigine blocked the late sodium current and exhibited closed-state channel block—properties that are conserved among class Ib blockers.[28,29] In published reports, mexiletine was found to inhibit late $Na_V1.5$ with potency 4.1–10.3-fold greater than the inhibition of peak current.[30] Lamotrigine exhibited 1.7–2.4-fold greater potency against late $Na_V1.5$ than at peak current.

At therapeutic exposure, whereas class Ib agents produce little to no effect on the electrophysiology or function of the heart; complications including slowing of conduction and depression of cardiac function can arise during inadvertent/purposeful overdose.[31] The biophysical properties of class Ib produce negligible effects on myocyte depolarization and confer reduced risk at resting heart rates in healthy myocardium.[32] In clinical trials, patients suffering from myotonia given mexiletine showed no change in cardiac conduction at therapeutic exposures comparable to efficacious antiarrhythmic treatment, supporting the lack of risk in healthy myocardium.[33] Furthermore, a double-blinded trial in patients treated for ventricular arrhythmias concluded that "in contrast to quinidine and the new class Ic antiarrhythmic agents, mexiletine also does not cause a marked increase in PR and QRS duration."[34] Mexiletine use has not been associated with sudden death, and one should not surmise that mexiletine has similar deleterious effects on the heart similar to that of class Ic agents.

Implications of the CAST trials for lamotrigine use in its current indications

The CAST trials demonstrated that in patients with non-life-threatening arrhythmias and a recent myocardial infarction (MI), administration of class Ic anti-arrhythmics significantly increased mortality compared with placebo. Lamotrigine, like mexiletine, exhibited class Ib-like properties. Importantly, neither lamotrigine nor mexiletine were studied in either CAST trial. As previously stated, lamotrigine is not indicated for treatment of cardiac arrhythmias. Anti-arrhythmics, including class I drugs, often carry a boxed warning in the United States based on CAST. To further explore the appropriateness of extrapolation of relative and absolute risks observed in the CAST trial, a descriptive epidemiological analysis was conducted using the IBM MarketScan Commercial, Medicare Supplemental and Multi-State Medicaid Databases to understand clinical characteristics of patient populations with non-life-threatening arrhythmias, epilepsy, and bipolar disorder. The insurance claims database contains individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, and Medicare and Medicaid programs. Using data from 2018, a cross-sectional descriptive analysis of key characteristics of patients with a prevalent diagnosis of epilepsy, bipolar disorder, and non–life-threatening cardiac arrhythmias was completed and found these patients with epilepsy and bipolar diagnoses were substantially younger than those with non-life-threatening cardiac arrhythmias (median age of 40 years vs. 60 years). The patients with epilepsy and bipolar also had a much lower prevalence of underlying cardiovascular diseases (38%–41% vs. 92%; data available upon request). This initial descriptive analysis raises concerns around direct extrapolation of results from CAST to very different patient populations without developing a more complete understanding of the underlying cardiac risk profile of patient subgroups within the epilepsy and bipolar patient populations of interest. However, the analysis suggests patients with epilepsy and bipolar disorder do have a significant prevalence of cardiovascular disease, and one meta-analysis published by the Centers for Disease Control suggests patients with epilepsy have higher rates of cardiac disease than patients who are not epileptic (Morbidity and Mortality Weekly Report 2013, 19% vs. 11%). Clinicians planning the use of lamotrigine in patients with epilepsy or bipolar disorder should therefore consider the potential therapeutic benefit against the possible risks in each individual before initiating treatment.

Lamotrigine has been globally marketed since the 1990s with an estimated exposure of >12 million patient-years. GlaxoSmithKline (GSK) routinely conducts proactive pharmacovigilance, including the screening of sources such as medical literature and aggregate review of postmarketing reports. To date, no serious cardiac events have been identified that warranted addition to the product label as adverse reactions. Nevertheless, based on the above in vitro findings, an amendment of the lamotrigine

prescribing information worldwide has been submitted to regulatory authorities in 2021 to advise caution in patients with clinically important structural or functional heart disease. Lamotrigine has a large safety database of 71,477 reports from global product launch to July 17, 2020, and the majority are related to skin reactions. Of 71,477 reports for lamotrigine, 1483 (0.021%) relate to the circulatory system. None of the events in the circulatory system have generated safety signals, apart from sudden death/sudden unexpected death in epilepsy (SUDEP).

Effect of lamotrigine on SUDEP

Patients with epilepsy, especially those with generalized seizures, are known to be at risk of SUDEP. It is suspected that seizures may have cardiovascular effects, such as changes in blood pressure, heart rate, and cardiac conduction, possibly leading to SUDEP. In 2011, GSK conducted a review of SUDEP that included data from lamotrigine clinical trials, published literature, and disproportionality analysis. This found no support for an increased risk of SUDEP associated with lamotrigine. A recently published population-based study, identifying all definite and probable cases of SUDEP from death certificate review; showed the importance of adherence to ASMs in reducing SUDEP risk.[35] Polytherapy of three or more ASMs reduced the risk of SUDEP by nearly 70% (adjusted odds ratio [OR]: 0.31, 95% confidence interval [CI]: 0.14–0.67). The reduction in SUDEP risk was 45% for lamotrigine containing regimens (OR: 0.55, 95% CI: 0.31–0.97 vs. a reference of no ASMs). No specific ASM was associated with increased risk, including the use of lamotrigine as monotherapy. This large series of adjudicated SUDEP cases found no evidence of lamotrigine being associated with an increased risk of sudden death.

Human cardiac conduction clinical safety

The first thorough QT/QTc study of lamotrigine was published in 2008[24] and further analyzed in 2011.[25] It examined the effects of lamotrigine in healthy subjects and found no increase in QTc interval, QRS duration, or blood pressure. There were small reductions in QTcF, small increases in heart rate and mean PR interval, but clinical experience has not identified any of these effects as relevant safety concerns.[36–39]

The current analysis showed no correlation between lamotrigine concentrations and change in QRS interval relative to baseline. However, there was a small increase in PR interval relative to baseline with increasing concentrations. At the highest values for peak concentrations reported in patients (i.e., ~20 μg/ml),[40] one would expect a PR prolongation of 8.24 ms relative to baseline, which is not likely to be clinically relevant. In fact, lamotrigine concentrations in over 95% of patients are expected to be below 15 μg/ml.[40] Additionally, this small degree of PR in the absence of QRS interval prolongation indicates lamotrigine does not cause clinically relevant $Na_V1.5$ blockade. Exposure to therapeutic dose levels of lamotrigine do not cause clinically relevant effects on atrioventricular conduction, depolarization, or repolarization. In humans, lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. In canines, extensive formation of a cardioactive 2-N-methyl metabolite is observed, which, as described in the US product insert, does cause dose-dependent effects on conduction in dogs. Similar cardiovascular effects are not anticipated in humans because only trace amounts (<0.6% of lamotrigine dose) have been found in human urine.

The findings from the TQT study are in stark contrast with nonclinical findings that suggest lamotrigine could produce significant sodium channel blockade at therapeutic doses. For example, the results from Harmer et al.[11] suggest that lamotrigine concentrations of 15 μg/ml would result in ~29% of the maximum effect of flecainide. Bergenholm et al. showed that the maximum effect of flecainide on QRS in humans is a 33.7 ms prolongation.[41] Under the assumption that all of flecainide's QRS effect is solely due to sodium channels, this would indicate a 9.8 ms QRS prolongation at a lamotrigine concentration of 15 μg/ml (free concentration of 6.6 μg/ml). In comparison, flecainide at therapeutic doses (190–200 mg) in 119 patients, 56 (47.1%) of which with structural heart disease, induced a QRS prolongation on average of 14 ms at rest and an average additional QRS prolongation of 9 ms when exercising (total average QRS prolongation from rest without flecainide to exercise with flecainide being 23 ms).[42] In combination, these referenced studies would suggest that therapeutic concentrations of lamotrigine would lead to a significant QRS prolongation, even at rest, and in those without structural heart disease.[11] The evidence of minor prolongation in PR and decrease in QRS intervals suggests that the in vitro study from Harmer et al.[11] translates poorly to the clinic. For the last decade, the product label has stated that QRS prolongation has been observed in lamotrigine overdoses. However, the limitations of those postmarketing overdose reports do not permit quantification of lamotrigine levels.

LIMITATIONS

Translation of $Na_V1.5$ block to physiologically relevant cardiac conduction slowing remains a challenge, which is evidenced by a lack of QRS prolongation in healthy subjects exposed to lamotrigine at/near the sodium channel

potency (IC_{50}). Unlike the extensive studies conducted to characterize the effects of hERG block to prolongation of cardiac repolarization (QTc), conduction liability remains enigmatic for several reasons, including the strong state-dependence of pharmacology and impact of underlying cardiac disease (functional and structural). As described, class Ib agents do not manifest appreciable PR/QRS prolongation until supra-therapeutic exposures are achieved—often in the setting of overdose; which have been addressed in the product label. Sensitizing in vitro systems to assess potential risk, such as the use of patient-derived stem cell cardiomyocytes or heterologous expression systems with mutant proteins, is an attractive option for risk assessment, but these approaches do not accurately recapitulate the human condition. Finally, our addition of a descriptive analysis of patient characteristics within a population-based commercial insurance claims analysis was not designed nor intended as a hypothesis testing study to explore the complex associations between ASMs, such as lamotrigine and cardiac conduction liability. This analysis was performed in the context of extrapolation of findings from the CAST randomized controlled trials in patients with arrythmias to a patient population with epilepsy to understand the appropriateness of this extrapolation.

CONCLUSION

In conclusion, based on in vitro biophysical properties similar to those of mexiletine, lamotrigine appears to produce weak $Na_V1.5$ block similar to known class 1b anti-arrhythmic agents. Based on the demographic differences described, the CAST results may not apply to lamotrigine or to the majority of patients for whom lamotrigine is indicated. In fact, at therapeutic doses, the observed electrophysiological properties of lamotrigine do not result in alteration of cardiac conduction that could be of clinical concern, as assessed by the evaluation of PR and QRS interval in a TQT study in healthy subjects. Yet, there is agreement that class Ib-like agents may carry risks for pro-arrhythmia, particularly in higher risk patients with clinically important structural or functional heart disease. Therefore, considering a lack of unequivocal clinical data against it, such caution should be considered for these higher risk subpopulations who are indicated lamotrigine for the treatment of epilepsy or bipolar disorder. These considerations do not imply the same risk level associated with class Ic anti-arrhythmic agents studied in the CAST trials that enrolled patients with cardiac disease and recent MI. The lamotrigine population is typically not post-MI and lamotrigine is not a class Ic agent manifesting similar potent sodium channel blockade.

AUTHOR CONTRIBUTIONS

L.I.T., S.C.V., S.P.O., O.D.P., C.W., M.C., L.R., S.F.S., V.P., J.A.C., A.B., and K.W.C. wrote the manuscript. L.I.T., A.B., and K.W.C. designed the research. L.I.T. performed the research. L.I.T., S.C.V., S.P.O., M.C., C.W., and K.W.C. analyzed the data.

ACKNOWLEDGEMENTS

The authors would like to thank John K. Finkle, MD. for his input and advice.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ingleby-Talecki L, van Dijkman SC, Oosterholt SP, et al. Cardiac sodium channel inhibition by lamotrigine: In vitro characterization and clinical implications. *Clin Transl Sci*. 2022;15:1978-1989. doi:10.1111/cts.13311