Diltiazem in Jervell and Lange-Nielsen Syndrome

Principle Investigator:

Prince Kannankeril, MD MSCI
Professor of Pediatrics
Division of Pediatric Cardiology
Vanderbilt Center for Arrhythmia Research and Therapeutics (VanCART)
Monroe Carell Jr. Children's Hospital at Vanderbilt
Vanderbilt University Medical Center

Sub-Investigators:

Frank A. Fish, MD
Professor of Pediatrics and Medicine
Vanderbilt Center for Arrhythmia Research and Therapeutics (VanCART)
Monroe Carell Jr. Children's Hospital at Vanderbilt
Vanderbilt University Medical Center

Dan Roden, MD
Professor of Medicine, Pharmacology, and Biomedical Informatics
Director, Oates Institute for Experimental Therapeutics
Senior Vice President for Personalized Medicine
Vanderbilt University Medical Center

M. Benjamin Shoemaker, MD, MSCI
Associate Professor of Medicine
Division of Cardiovascular Medicine, Department of Medicine
Vanderbilt Center for Arrhythmia Research and Therapeutics (VanCART)
Vanderbilt University Medical Center

Yuko Wada, MD
Research Instructor, Clinical Pharmacology
Vanderbilt Center for Arrhythmia Research and Therapeutics (VanCART)
Vanderbilt University Medical Center

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1.0 Background

Jervell and Lange-Nielsen (JLN) syndrome is a rare inherited arrhythmia syndrome characterized by severe QT prolongation, bilateral sensorineural hearing loss and risk of ventricular arrhythmias and sudden death. It is a severe form of congenital long QT syndrome (LQTS) caused by homozygosity or compound heterozygosity in *KCNQ1* or *KCNE1*, the 2 subunits of the slow delayed rectifier potassium current (I_{Ks}). Fifty percent of individuals with JLNS have cardiac events before 3 years of age and more than half of untreated children with JLN die before 15 years of age.[1]

1. Tranebjærg L, Samson RA, Green GE. Jervell and Lange-Nielsen Syndrome. 2002 Jul 29 [updated 2017 Aug 17]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2024. PMID: 20301579.

2.0 Rationale and Specific Aims

Beta-blockers are the cornerstone of therapy in LQTS, but have only partial efficacy in JLN, with 51% of JLN patients having arrhythmic events despite therapy and 27% on therapy who suffer cardiac arrest or sudden death.[2] The median age at death on therapy was 8 years (IQR, 6 to 14). Additional therapies are clearly needed for this rare disease.

Wada et al used induced pluripotent stem cell-derived cardiomyocytes from a JLN patient to demonstrate severe action potential duration (APD, the cellular correlate of the QT interval) prolongation.[3] While this is expected, due to genetic loss of I_{Ks}, pharmacologic block of I_{Ks} minimally prolonged APD in control cells. Dr. Wada has new evidence that L-type Ca channel (LTCC) current is significantly increased in JLN cells compared to control cells, and that the calcium channel blocker diltiazem significantly shortens APD at low therapeutic concentrations. Diltiazem does not block I_{Kr} at therapeutic concentrations unlike other calcium channel blockers like verapamil, which may prolong the QT interval. This suggests diltiazem may be a useful therapeutic agent specifically in JLN syndrome. Therefore, we aim to test the following hypothesis in humans:

Specific Aim: To test the hypothesis that IV diltiazem acutely shortens the QT interval in human(s) with the Jervell-Lange Nielsen syndrome.

2. Schwartz PJ, Spazzolini C, Crotti L, et al. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. Circulation. 2006 Feb 14;113(6):783-90. PMID: 16461811.
3. Wada Y, Wang L, Hall LD, Yang T, Short LL, Solus JF, Glazer AM, Roden DM. The electrophysiologic effects of KCNQ1 extend beyond expression of IKs: evidence from genetic and pharmacologic block. Cardiovasc Res. 2024 Epub ahead of print. PMID: 38442735.

3.0 Animal Studies and Previous Human Studies

The ability of a drug to shorten the QT interval acutely has been successfully extrapolated to chronic beneficial effects in various forms of the long QT syndromes. Mexiletine IV shortened the QT interval by 116 +/- 50 ms in 15 LQT3 patients, and the QT interval was also shortened by chronic oral mexiletine in a subset of patients.[4] IV potassium was infused in 7 LQT2 patients, showing a 24% reduction in QTc (from 617 to 469 ms),[5] and chronic oral potassium shortens QTc in LQT2 patients.[6] Both mexiletine and supplemental potassium are now used as additional therapies in LQT3 and LQT2 respectively. Here we propose a similar line of investigation for diltiazem in JLN syndrome.

Diltiazem is an oral and parenteral nondihydropyridine calcium channel antagonist, approved by FDA for atrial arrhythmias, hypertension, and angina. Primarily, diltiazem inhibits the flow of calcium ions through

the LTCC into cardiac muscle during depolarization. Diltiazem is a negative inotrope and negative chronotrope. Along with coronary artery vasodilation, the combination decreases myocardial oxygen demand resulting in decreased heart rate. The standard initial IV dose is 0.25 mg/kg over 2 minutes. If needed, a repeat dose of 0.35 mg/kg can be given after 15 minutes. No renal or hepatic dose adjustment is necessary.[7]

4. Funasako M, Aiba T, Ishibashi K, et al. Pronounced Shortening of QT Interval With Mexiletine Infusion Test in Patients With Type 3 Congenital Long QT Syndrome. Circ J. 2016;80(2):340-5. PMID: 26632536.
5. Compton SJ, Lux RL, Ramsey MR, et al. Genetically defined therapy of inherited long-QT syndrome. Correction of abnormal repolarization by potassium. Circulation. 1996 Sep 1;94(5):1018-22. PMID: 8790040.
6. Etheridge SP, Compton SJ, Tristani-Firouzi M, Mason JW. A new oral therapy for long QT syndrome: long-term oral potassium improves repolarization in patients with HERG mutations. J Am Coll Cardiol. 2003 Nov 19;42(10):1777-82. PMID: 14642687.
7. Talreja O, Cassagnol M. Diltiazem. 2023 Aug 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30422532.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria

- Age > 18 years
- Genetically confirmed diagnosis of Jervell and Lange-Nielsen syndrome
    - Homozygous or compound heterozygous for variants in *KCNQ1/KCNE1*
    - QT prolongation on ECG
    - Sensorineural hearing loss
- Able to provide written informed consent

Exclusion Criteria

- Known hypersensitivity to diltiazem
- Pregnancy
- Congestive heart failure, angina, preexcitation, or COPD
- Sick sinus syndrome or AV block in the absence of a pacemaker/defibrillator
- Any clinically significant ongoing medical or surgical condition that might jeopardize the subject's safety or interfere with the conduct of the study in the judgement of the investigator
- Baseline systolic blood pressure <100 Hg or diastolic blood pressure < 60 Hg

5.0 Enrollment/Randomization

Eligible subjects will be enrolled by study personnel. Due to the rarity of JLN syndrome, there are only 2 eligible subjects currently followed at VUMC. We anticipate enrolling a single subject, but will seek approval for additional subjects.

6.0 Study Procedures

General Approach: This is a prospective proof-of-concept trial that will enroll eligible patients with JLN and test the hypothesis that diltiazem IV will result in QT shortening. Subjects will be recruited by study personnel and will be scheduled for a single outpatient CRC visit. On the day of the visit, written informed consent will be obtained, a urine pregnancy test will be obtained for those subjects who are able to be pregnant, and the subject's weight and blood pressure will be recorded. If baseline SBP is < 100 mm Hg or DBP < 60 mm Hg, the study will be terminated. Otherwise, a peripheral IV will be inserted and diltiazem doses ordered to the bedside. If an implanted cardiac device (pacemaker or ICD) is in place, it will be interrogated to ensure no recent rhythm abnormalities. Just prior to administering diltiazem, an ECG and BP will be obtained. A single dose of I.V. diltiazem (0.25 mg/kg over 2 minutes) will be administered with 12-lead ECG and BP obtained at 2, 5, 7, 10, 15 and 20 minutes. If at 10 minutes there has been no QT shortening, and the SBP is stable

(<20% drop from baseline and > 100 mm Hg) a repeat dose (0.35 mg/kg) will be given at 15 minutes, with 12-lead ECG and BP obtained at 17, 20, 22, 25, 30 and 35 minutes (see Table below). After 20 minutes (single dose) or 35 minutes (2 doses), the test will end and the subject will remain in the CRC monitored on continuous telemetry for 2 hours. Prior to CRC discharge the IV will be removed. The primary analysis will be a repeated measures (paired) comparison of the QTc at baseline and following diltiazem. As JLN is a very rare disease, we anticipate enrolling only 1 or perhaps 2 subjects, as that represents the total number of subjects followed at VUMC.

Prior to Enrollment	Patient recruited in clinic or by phone
	Patient will continue all outpatient medications prior to study. Specifically, beta-blocker therapy will not be stopped for this study.
8:00 AM	Arrive to Clinical Research Center (CRC)
	Sign consent form, obtain weight, BP, urine pregnancy test
8:15 AM	Place peripheral I.V., order diltiazem (0.25 mg/kg and 0.35 mg/kg doses) to bedside
8:30 AM	Interrogate Device if present
	Obtain baseline ECG and BP just prior to diltiazem
	Sample Timetable with 1 dose
9:00 AM	Administer IV diltiazem (0.25 mg/kg) over 2 minutes
9:02 AM	2 min ECG and BP
9:05 AM	5 min ECG and BP
9:07 AM	7 min ECG and BP
9:10 AM	10 min ECG and BP
9:15 AM	15 min ECG and BP
9:20 AM	20 min ECG and BP
	End test
+2:00 hours	Monitored rest period. Patient remains on the CRC
	Sample Timetable with 2 doses
	Obtain baseline ECG and BP just prior to diltiazem
9:00 AM	Administer IV diltiazem (0.25 mg/kg) over 2 minutes
9:02 AM	2 min ECG and BP
9:05 AM	5 min ECG and BP
9:07 AM	7 min ECG and BP
9:10 AM	10 min ECG and BP – If no QT shortening and BP stable, prepare second dose
9:14 AM	14 min ECG and BP
9:15 AM	Administer IV diltiazem (0.35 mg/kg) over 2 minutes
9:17 AM	17 min ECG and BP
9:20 AM	20 min ECG and BP
9:22 AM	22 min ECG and BP
9:25 AM	25 min ECG and BP
9:30 AM	30 min ECG and BP
9:35 AM	35 min ECG and BP
	End test
+2:00 hours	Monitored rest period. Patient remains on the CRC

7.0 Risks

Risks associated with diltiazem include hypotension, bradycardia, dizziness, flushing, fatigue, headaches and edema. Many of these risks are mitigated by the IV dosing, with peak effect in 2-5 minutes after bolus dosing. We expect a slight decrease in blood pressure, as a decrease in SBP and DBP of 17 and 13 mm Hg was observed in clinical studies. Hypotension was observed in 9-16% of individuals given diltiazem for

conversion of SVT or atrial fib/flutter.[8,9] We expect less hypotension given to subjects in sinus rhythm. For safety, diltiazem will not be given if the baseline SBP is < 100 mm Hg, or DBP < 60 mmHg.

8. Dougherty AH, Jackman WM, Naccarelli GV, Friday KJ, Dias VC. Acute conversion of paroxysmal supraventricular tachycardia with intravenous diltiazem. IV Diltiazem Study Group. Am J Cardiol. 1992 Sep 1;70(6):587-92. PMID: 1510006.

9. Goldenberg IF, Lewis WR, Dias VC, Heywood JT, Pedersen WR. Intravenous diltiazem for the treatment of patients with atrial fibrillation or flutter and moderate to severe congestive heart failure. Am J Cardiol. 1994 Nov 1;74(9):884-9. PMID: 7977118.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others:

Definitions of adverse events: an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment or study protocol.

Adverse events include:

- Worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- Patient / subject deterioration due to the primary illness
- Intercurrent illnesses
- Drug interactions
- Events related or possibly related to concomitant medications
- Abnormal laboratory values or changes of vital signs, as well as significant shifts from baseline within the range of normal, which the Investigator considers clinically significant.

Unexpected Adverse Drug Reaction: an unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. Definitions of serious adverse events or serious adverse drug reaction: during clinical investigations, adverse events may occur which, if suspected to be drug-related (adverse drug reactions), must be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function.

A serious adverse event/experience (SAE) or reaction is any untoward medical occurrence that:

1. results in death
2. is life-threatening
3. requires inpatient hospitalization or prolongation of existing hospitalization
4. results in persistent or significant disability/ incapacity (as per reporter's opinion)
5. is a congenital anomaly/birth defect
6. is another medically important condition
7. The term "life-threatening" in the definition of "serious" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical conditions that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Definition of severity of adverse events:

Mild: Causing no limitation of usual activities; the subject / patient may experience slight discomfort.

Moderate: Causing some limitation of usual activities; the subject / patient may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject / patient may experience intolerable comfort or pain.

Definition of adverse event causality:

The Investigator will determine causality of each adverse event by using the classification criteria: unlikely, likely, or not assessable.

Unlikely: The AE is considered by the Investigator to be due to a pre-existing condition, a known manifestation of the target disease, a recurrent condition, or is likely explained by environmental or diagnostic therapeutic factors or was pre-existing and did not deteriorate.

Likely: The AE occurred during or after administration of the study treatment or a pre-existing event worsened within an appropriate period of time, and at least one of the following criteria is applicable:

- the event could not be explained by the clinical condition or history of the subject, environmental or toxic factors, or other diagnostic or therapeutic measure;
- was an expected ADR associated with study treatment or a class-labeled drug effect;
- AE subsided or disappeared after withdrawal or dose reduction of study treatment; or
- AE recurred after re-exposure to study treatment.

Not assessable: There is insufficient or conflicting evidence for classifying the causality of the AE as likely or unlikely. Lack of information may apply for this situation.

Note: AEs with causality 'likely' or 'not assessable' are considered to be 'possibly drug-related.'

Adverse event reporting

Any adverse events (AEs) will be reported to the PI within 72 hours of notification of the event. The PI will notify the IRB of any major adverse events. Any unanticipated problems involving risk to the participants or others will be discussed with the PI and IRB. Non-serious AEs and incidences of noncompliance with the protocol will be reported to the IRB at the time of annual review.

Serious Adverse Events (SAEs) will be reported according to the following procedure:

The occurrence of serious adverse events will be reported to the Investigator within 24 hours after notification of their occurrence. The Investigator will report SAEs to the Vanderbilt Institutional Review Board within 7 days of the Investigator’s notification of the event.

In an unanticipated event of prolonged side effect, requiring prolongation of hospital stay, patients will be retained in the hospital until side effects have resolved. For minor side effects, where inpatient care is deemed unnecessary, follow- up will be maintained via phone or as outpatient if necessary. Patient and their families will be given the PI’s contact number for reporting any other effects of medication following discharge.

Any newly discovered information which may affect the subject or their caregiver's decision to continue to participate in the study will be passed on to them as soon as possible. This may also result in a change to the consent form and review by the IRB.

9.0 Study Withdrawal/Discontinuation

Participants may withdraw from the study at any time by informing the study staff verbally or in writing. If an individual withdraws their consent, we will withdraw the participant. Contact information for the PI and study staff will be made available to the participant upon enrollment in the consent document. Any remaining biological samples and data will be destroyed. Any data or biological samples that have been used for research prior to their withdrawal request will not be withdrawn and destroyed.

A participant may be withdrawn from the study by the PI if any of the following occurs:

i. A procedural complication occurs prior to completion of the study protocol that requires the study procedure to be aborted, or precludes collection of study data.

ii. The patient becomes hemodynamically unstable for any other reason that requires the study procedure to be cancelled prior to completion of the study protocol, or precludes the collection of study data

iii. The primary operator determines it is in the patient's best interest to forego completion of the study protocol

10.0 Statistical Considerations

This is a proof-of-concept study testing the hypothesis that diltiazem will shorten the QT interval in JLN syndrome, a very rare disease. It is likely we will recruit a single subject. Thus we anticipate simply presenting the heart rate, QT, and QTc before and after IV diltiazem. BP will be monitored for safety.

11.0 Privacy/Confidentiality Issues

We describe here mechanisms in place at Vanderbilt through IRB policy to protect against such risks; these apply to all studies described below. All records are retained on password-protected computers accessible only to members of the study team. Computers containing these records are only connected to networks if they include appropriate firewalls and security measures. The identity of any individuals and their families are not to be revealed in any publication without their written informed consent.

12.0 Follow-up and Record Retention

The expected duration of this study is estimated to be 1 year. The study results will be retained for at least six years after the study is completed. At that time, the research information not already in the medical record will be destroyed.