Ranolazine in LQT3 Patients

I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose of the study. The purpose of this study is to determine whether late sodium channel blockade might be effective in shortening the QTc interval in various LQT3 mutations and be considered as a safe therapeutic option for LQT3 patients.

Background. Long QT syndrome (LQTS) is a genetic disorder characterized by prolongation of the QT interval in the electrocardiogram (ECG) and a propensity to torsade de pointes ventricular tachycardia frequently leading to syncope, cardiac arrest, or sudden death usually in young otherwise healthy individuals (1,2). The long QT syndrome is caused by mutations of predominantly potassium and sodium ion channel genes or channel-related proteins leading to positive overcharge of myocardial cell with consequent heterogeneous prolongation of repolarization in various layers and regions of the myocardium (3-5). These conditions facilitate the early afterdepolarization and reentry phenomena underlying development of polymorphic ventricular tachycardia observed in patients with LQTS (6).

The most common types of LQTS affect: the slow delayed rectifier potassium repolarization channel (KCNQ1; LQT1) resulting in a reduction in IKs current; the rapid delayed rectifying potassium repolarization channel (KCNH2; LQT2) resulting in a reduction in IKr current; and the sodium channel (SCN5A; LQT3) resulting in an increase in late INa current (7,8). Among positively genotyped patients, LQT1 and LQT2 account for about 90% of LQTS cases, whereas LQT3 accounts for about 5% to 8% of cases (7,8). The remaining types of LQTS are extremely rare, although they contribute tremendously to our knowledge of the repolarization process. The significant number of LQT1 and LQT2 patients among LQTS patients contributed to more advanced understanding of phenotypic characterization and phenotype-genotype associations. The number of patients with the LQT3 form of the disease is proportionally smaller and studies conducted to date are rather small and focused predominantly on single gene mutation or single pedigree (9-12). Nevertheless, increased awareness of the LQTS among physicians and patients leads to a growing number of patients who are evaluated for the diagnosis of the LQTS and therefore the number of LQT3 patients is increasing too (8).LQT3 patients represent a challenging cohort of patients. Unlike patients with LQT1 and LQT2 form of this disorder, the LQT3 patients have high lethality of cardiac events with 1 in 5 patients dying suddenly during their first syncopal/arrhythmic event (Figure 1) (3,13).

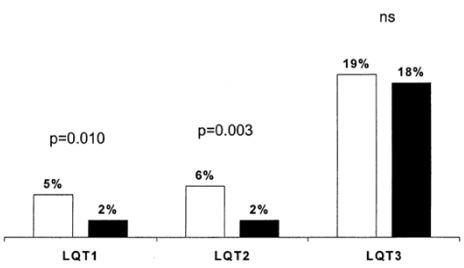

Figure 1. The lethality of cardiac events analyzed by sex in long QT syndrome (LQTS) family members with known genotype. Open bars - males; black bars - females. P<0.001 when comparing LQT3 males and females to LQT1 and LQT2 males and females, respectively (Zareba 2003; reference 13).

As shown in Figure 2 for childhood (age 0-18) in the analysis of 1404 patients, LQT3 was found to be associated with significantly higher risk of aborted cardiac arrest or death than LQT1 and LQT2 (14). A similar pattern is observed in LQTS patients after age 40 in whom LQT3 patients show the highest risk.

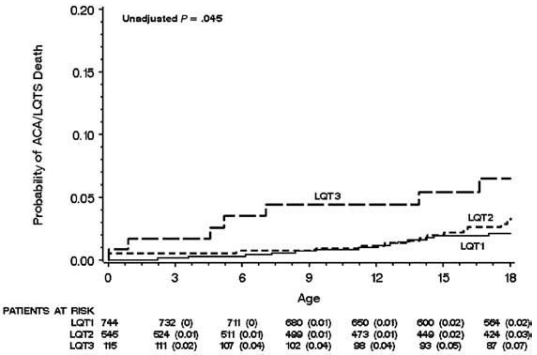

Figure 2. The cumulative probability of aborted cardiac arrest or death in LQTS children (age 0-18 years) by genotype (Goldenberg 2008; reference 14).

Optimal therapy in LQT3 patients remains controversial. Data published in 2000 from the International LQTS Registry (15) did not support beneficial effects of beat-blockers in LQT3 patients, although only 28 LQT3 patients were available for analysis at that time. Recent analysis by Schwartz et al. (16) of 33 LQT3 patients (of whom 18 where on therapy) provide further indication that beta-blockers do not seem beneficial and that an implantable cardioverter-defibrillator (ICD) is not the solution for all LQT3 patients. There is a need for establishing criteria for determining which LQT3 patients might benefit from prevention of sudden death with ICD. At the same time further investigations toward use of sodium current blockers in LQT3 patients seem justified.

There are preliminary data showing that sodium current blockers shorten QTc duration in LQT3 patients. Several sodium current blockers were tested: Schwartz et al. (17) demonstrated that mexiletine could be an option for LQT3 patients but gastro-intestinal side effects limit long-term use of this compound. We tested flecainide (18) documenting that low doses of these drugs are effective in shortening QT and subsequently we showed long-term effectiveness of this drug in QT shortening. However, as documented in a study by Benhorin et al. (11), QRS widening was observed in LQT3 patients receiving flecainide. Priori et al. (19) showed that flecainide may induce ST segment elevation in LQT3 patients, further raising concerns about the safety of flecainide therapy.

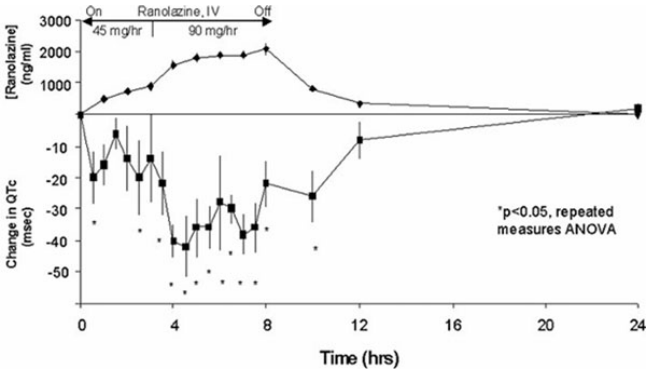

Figure 3. Effect of ranolazine intravenous administration on QTc in LQT3 patients (Moss 2008).

Our recent data from a pilot study conduced in 5 patients with delta-KPQ mutation demonstrated that late sodium current blockade with ranolazine, a compound that does not affect sodium peak current and therefore does not changes QRS duration and morphology, is very effective in shortening QTc in LQT3 patients (20). This innovative therapy might serve as potential solution for treatment of LQT3 patients. However, there are very limited data on their effectiveness and long-term safety. Late sodium current blockade with ranolazine might be a safer option since peak sodium current and QRS duration are not affected by this class of the drugs. However, apart from a 5-patient study with acute intravenous administration of ranolazine (20), there are no data on long-term benefits and safety of oral use of this compound.

Expression Studies with Ranolazine Administration

As non-clinical part of the project we will determine in in vitro expression studies whether the functional defects caused by the LQT3 mutations can be reversed by ranolazine mutation (21). We will test whether ranolazine causes a decrease in late sodium current, slower recovery from inactivation and/or changes in time course of inactivation, ameliorating the causative functional

effect of each individual mutation. We expect that for mutations that show an increase in late sodium current this increase will be blocked by the drug without an increase in peak current. For the I1768V mutant, no increase in persistent current was observed in previous functional studies (22). Nonetheless, because ranolazine is thought to act in the inactive state of the channel (22, 23), we expect the faster recovery from inactivation caused by this and other mutations to be reversed by the drug as shown for the R1623Q mutant channel (23). For two of the mutants (F1617del and T370M), the functional defect is not known and ranolazine may not be able to reverse their effect. A dose response of ranolazine (1-300 μM) will be measure for each of the mutants to test for mutation specific changes in the efficacy of the drug.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

Number of subjects. The expected enrollment in Study 1 is 30 subjects. The expected enrollment in Study 2 is 30 subjects. Subjects are welcome to participate in both studies, if interested and eligible.

Gender of Subjects. There are no gender-based enrollment restrictions.

Age of Subjects. The age range of subjects is 21 years of age and older

Racial and Ethnic Origin. There are no racial or ethnic restrictions.

Inclusion Criteria:

- ≥ 21 years of age
- Genotyped positive for an LQT3 gene mutation
- Not currently taking an antiarrhythmic drug (beta blockers are allowed)

Exclusion Criteria:

- Age at enrollment is < 21 years of age
- Has not had genetic confirmation of LQT3 mutation
- Significant co-morbidity that would preclude the subject's safe participation in this study
- Pregnancy or women of child-bearing age not using an acceptable method of birth control (i.e.: oral contraceptives, barrier method (condom AND diaphragm combined with spermicide. A diaphragm or condom alone is not considered adequate contraception.) implants; injections; IUD or abstinence)
- Nursing mothers
- Evidence of prior sensitivity to ranolazine
- Hepatic or renal disease that might adversely affect ranolazine excretion
- Currently taking Strong CYP3A Inhibitors (including: ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir and saquinavir)
- Currently taking CP-gp inhibitors (including: cyclosporine)
- Currently taking CYP3A Inducers (including: rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine and St. John's wort)
- Evidence for no effect of ranolazine on late sodium current kinetics in in vitro testing for specific mutation or evidence for repolarization

prolongation in in vitro testing of specific mutation.

Therapeutic modifications:

- Moderate CYP3A inhibitors (including: diltiazem, verapamil, and erythromycin): Limit ranolazine to 500 mg twice daily
- CYP3A substrates: Limit simvastatin to 20 mg when used with ranolazine.
- Drugs transported by P-gp or metabolized by CYP2D6 (e.g. digoxin, tricyclic antidepressants): May need reduced doses of these drugs when used with ranolazine

Vulnerable Subjects. This study may involve some elderly subjects. Extra care will be paid in order to ensure their understanding of this research.

III. METHODS AND PROCEDURES

Study 1: Short-term Ranolazine Administration. We will administer this drug orally to determine the effect of ranolazine on QTc duration as well as other ECG, echocardiogram and Holter-derived parameters.

The patients will be invited to stay at the General Clinical Research Center (GCRC).

On day 1, the subject will have baseline ECGs recorded hourly, an echocardiogram and 24-hour Holter recording as well as bedside ECG monitoring continuously. Laboratory test will be performed to determine creatinine clearance. On day 2, the subject will receive 1000 mg of ranolazine orally and will have repeat ECG recordings, an echocardiogram 4-6 hours after dosage is given, and Holter monitoring and bedside monitoring continuously as well as hourly sampling of plasma concentration of ranolazine. Ranolazine reaches peak plasma concentration after oral administration in about 4-6 hours. We will also evaluate the effects of ranolazine on novel ECG, echo and Holter-derived markers to determine whether they could be even more sensitive regarding effects of drug on repolarization and its dynamics.

The study will remain under scrutiny of the Data Safety Monitoring Board (Sabu Thomas M.D. 585-275-2475). The Clinical Principal Investigator or representative will monitor the safety of the subject as well as any adverse events (Clinical P.I. Spencer Rosero, M.D. 585-275-4775).

All ECGs and Holter recordings will be read blindly by the central ECG Core Lab.

Remaining conservative, we expect that recruitment and testing of these patients will be scheduled to occur over 2 years.

Study 2: Long-term Ranolazine Administration. The long-term effectiveness of ranolazine will be investigated in 30 subjects representing at least 3 different LQT3 mutations, by administering matching placebo for 30 days and ranolazine 2x1000mg for 150 days. Subjects will have ECG and Holter recording at baseline, 1 month, 3-7 days after start of ranolazine, 2 month, and 6-month time points. At baseline, laboratory test will be performed to determine creatinine clearance, unless this result is already available if subject participated in the Study 1. Data regarding possible side effects of the drug as well as clinical events will be collected.

Enrollment in Study 2 will be limited to subjects with mutations for which the effect of ranolazine has been studied, and the data analyzed for safety, in either Study 1 or in our prior IV ranolazine drug study. In practice this will involve enrolling one subject with an unstudied mutation into Study

1, testing the effects and safety of ranolazine on that mutation, and then moving on to enrolling that subject or other subjects with that specific mutation into Study 2.

Exam One has been contracted by the University of Rochester to perform home visits for administering ECGs and Holter monitors and to collect baseline blood specimens (for creatinine testing for all participants and for pregnancy testing for women of reproductive age) for research purposes. All Exam One personnel have been trained in HIPAA compliance and are bound by the privacy practices of that company. NIH human subject protection training will be required of all personnel who have contact with study participants. Study-specific procedural training will be provided, including specific instructions for lead placement for ECGs and Holters and for reporting of safety concerns. Exam One can insure via their event management system that every examiner that performs services for this study has their standard training, NIH human subject protection training, and reviews protocols specific to the related assessment services. A schedule of regular conference calls and a reporting system will be established for monitoring of study visits including any problems encountered.

The study will remain under scrutiny of the Data Safety Monitoring Board (Sabu Thomas, M.D. 585-275-2475). The Clinical Principal Investigator or representative will monitor the safety of the subject as well as any adverse events (Clinical P.I. Spencer Rosero, M.D. 585-275-4775).

All ECGs and Holter recordings will be read blindly by central ECG Core Lab.

Shortening of QTc observed at 2 and 6 months in comparison to baseline and 1-month time points will be the primary endpoint of the study. We will also evaluate long-term effect of ranolazine on several novel ECG parameters reflecting repolarization morphology and dynamics, as mentioned above.

It is hypothesized that the difference between the 2-month and baseline ECG as well as the 6-month and baseline ECG will be significantly different compared to the difference between the 1-month (placebo) ECG and baseline. Assuming a 40ms standard deviation in studied LQT3 patients, sample size of 30 patients will provide 90% power to detect at least 18 ms difference in QTc between ranolazine and baseline. It will provide 98% power if the difference is in the order of 40 ms as observed in our prior study.

DATA MANAGEMENT. Data will be entered into our web-based, password-protected clinical data-management system. This data will be verified via a system of checks, queries and ranges to ensure accuracy. Some data checks are implemented during data entry, preventing some errors altogether and immediately prompting for resolution of other errors. Other checks are performed daily and weekly yielding high quality data within strict timelines.

DATA ANALYSIS. Routine patient clinical data, data forms, questionnaires, consent forms and any other correspondence will be maintained using our existing data management systems in the Heart Research Follow-up Program

DATA STORAGE. All study documents will be kept in a locked file room. All computers are password-protected and kept in a locked area.

IV. RISK/BENEFIT ASSESSMENT

Risk Category. This research is of greater than minimal risk.

Potential Risk. The potential risks associated with the study are:

Ranolazine
The most commonly reported side effects in both healthy volunteers and patients have been: dizziness, headache, nausea, fatigue, constipation, indigestion, peripheral leg or ankle swelling, chest pain, coughing, breathlessness, palpitations, abdominal pain, vomiting, and dry mouth.

The following serious side effects may be related to ranolazine and have occurred in people with heart disease: heart attack; fatal or life-threatening heart beat or rhythm (irregular, fast or slow); fainting or loss of consciousness, a spinning sensation; sweating; ringing/buzzing noise in the ear; abnormal lab tests related to the kidney, and involuntary muscle contractions. Higher doses of ranolazine have caused low blood pressure particularly when people rise from a lying or sitting position. Fainting, changes in vision, a burning or tingling feeling – in the legs, drowsiness, and confusion and disorientation have also been reported.

If the subject is taking digoxin, he will be instructed to decrease the dose of digoxin in half since ranolazine increases the level of digoxin in blood. The increase of blood level of digoxin might be associated with cardiac arrhythmias.

Electrocardiogram (ECG) & Holter Monitor Risks and Discomforts
There may be skin irritation from the gel or adhesive used to apply the electrodes.

Echocardiogram (ECHO)

Subjects will undergo two separate echocardiograms. Images will be digitized and stored to optical disk for subsequent analysis off-line. The following views will be obtained:

- Parasternal long axis (including zoom frame of LV outflow tract)
- Parasternal short axis (papillary muscle level)
- Apical 4-chamber
- Apical 2-chamber
- Apical 3-chamber
- Color Tissue Doppler imaging in the apical 4, 2, and 3 chamber views, (one 3-beat loop of each)
- Pulsed-wave Doppler of mitral inflow from apical 4-chamber view
- Pulsed-wave Doppler of pulmonary venous flow from apical 4-chamber view
- Pulsed wave Doppler from the L VOT
- Tissue Doppler tissue imaging of septal and lateral mitral annulus from apical 4-chamber view

The following parameters will be measured or calculated at each time point:

- LV End-diastolic Volume/Index
- LV End-systolic Volume/Index
- Calculated L VEF = 1- LV End-systolic Volume/ LV End-diastolic Volume ratio
- LV Stroke Volume = LV Diastolic Volume - LV Systolic Volume
- Visually estimated LV Ejection fraction
- L V Global Strain (calculated from 2D strain images)
- Myocardial Performance Index
- Mitral E wave Velocity
- Mitral A wave Velocity
- Mitral E/ A ratio

- Mitral E wave deceleration time
- LV Isovolumic Relaxation Time (LV IVRT)
- Mitral Annular Velocity (Myocardial relaxation velocity (E')
- Mitral E wave Velocity/Mitral Annular Velocity ratio (EIE')
- Systolic Annular Velocity
- Pulmonary Vein S wave Velocity
- Pulmonary Vein D wave Velocity
- Pulmonary Vein S wave/ D wave velocity ratio *(SID)*
- LV Dyssynchrony score (ms)

An echocardiogram will be performed at the following time points:

- Day 1
- Day 2: 4-6 hours after ranolazine dose is given

Intravenous (IV) Line
An intravenous (IV) line will be inserted for the purpose of blood sampling. There may be some minor discomfort, pain, redness, bruising or bleeding at the site of the needle puncture.

Pregnancy
There may be risks to the mother (or to an embryo, fetus or nursing infant) that are currently unknown or unanticipated. The subject must use a medically approved method of birth control, (i.e.: oral contraceptives; barrier method (condom AND diaphragm combined with spermicide. A diaphragm or condom alone is not considered adequate contraception.) implants; injections; IUD or abstinence).

Risks associated with Home Visits
Any evidence of child abuse or neglect or suspicion that a person may present a danger of harm to others or self that is observed during home visits is required to be reported to the appropriate authorities.

Potential Benefits to the Subjects. The subject may or may not benefit from this study.

Alternatives to Participation. The alternative is not to participate.

V. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

Method Of Subject Identification And Recruitment. Most subjects will be recruited from the Long QT Registry at the University of Rochester.

Process of Consent. Study 1: Subjects will be consented in the GCRC by a study team member. Study 2: If the subject participated in Study 1, he may be consented into Study 2 before he is discharged. Otherwise, subjects will be consented by a team member at/near the subject's home or by mail.

In both studies, the subject will sign two identical consent forms. He will retain one for his records and the other will be kept in the locked file-room in the Heart Research Follow-Up Program.

Costs to the Subject. Study 1: The subject may incur some nominal costs in his travels to the University of Rochester. These costs may include: driving to the airport, parking, meals on traveling days. He will be reimbursed for these expenses upon supplying receipts. Airline tickets,

possible hotel stay while in Rochester, and travel to/from the Rochester International Airport as well as travel from the hotel to/from the University of Rochester will be provided. Study 2: There are no expected costs to the subject.

Payment for Participation. Study 1: $300/day ($600 maximum); Study 2: $200/month ($1200 maximum)

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