Ten-year experience in atenolol use and exercise evaluation in children with genetically proven long QT syndrome

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Abstract

Background: Due to its availability, atenolol is the primary beta-blocker used in Australia for children with long QT syndrome. There is limited data on long-term follow-up of its use. Methods: A single-tertiary-center, retrospective, observational study investigating all children and adolescents who had genetically proven long QT syndrome type 1 (LQT1) and type 2 (LQT2) was conducted. Their pretreatment exercise tests were evaluated for QTC intervals into the recovery phase of exercise. Results: Eighty-six patients were identified (LQT1, 67, and LQT2, 19) from 2004 to 2014. The majority (86%) of patients were initially referred for family screening. Atenolol was administered at a mean dose of 1.58 ± 0.51 mg/kg/day. During the median follow-up period of 4.29 years, only one proband developed ventricular arrhythmia whilst taking atenolol. No patient had cardiac arrest or aborted cardiac arrest. With respect to side effects of atenolol, only two patients had intolerable side effects necessitating changes of medication. Evaluation of exercise tests (pretreatment) demonstrated that corrected QT (QTC) intervals at 2-3 min into the recovery phase of exercise were significantly prolonged for LQT1 patients. LQT1 patients with transmembrane mutation had longer QTc intervals than their C-terminus mutation counterparts, reaching statistical significance at 3 min into the recovery phase of exercise. Conclusions: Atenolol is an effective treatment for genetically proven LQT1 and LQT2 children and adolescents, with good tolerability. In LQT1 patients, QTc intervals at 2-3 min into the recovery phase of exercise were significantly prolonged, particularly in patients with transmembrane mutations.

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1. Introduction

Data on the use of atenolol for long QT syndrome (LQTS) in children are sparse. Atenolol is the primary beta-blocker used in Australia for LQTS patients. Nadolol is not marketed in Australia and is not readily available. This study aimed to review the use of atenolol for children and adolescents with genetically proven LQTS type 1 (LQT1) and type 2 (LQT2). In addition, we also re-evaluated all the exercise tests performed for these patients, as exercise tests were undertaken routinely at the Royal Children's Hospital (RCH), Melbourne, which included measurement of corrected QT (QTC) intervals at 10 min into the recovery phase of exercise. Around one-third of genetically proven LQTS patients have a normal QTc interval measurement at rest. An exercise test is useful in identifying LQTS patients who are suspected clinically but present with a normal electrocardiogram (ECG) at rest [1-4]. The relationship with targeted mutation site-specific differences in LQTS is unclear. A single-tertiary-center retrospective observational study investigating all children and adolescents who have genetically proven LQT1 and LQT2 was therefore conducted.
2. Materials and methods

2.1. Methodology

A retrospective observational study was performed with the approval by the Research Ethics Committee of RCH, Melbourne, Australia. Data were collected from all patients with genetically proven LQT1 and LQT2 (genotype-positive for LQT1 (KCNQ1) or LQT2 (KCNH2) genes). Genetic reports of all patients were reviewed again by a genetic scientist (PSJ) to confirm that all patients in our cohort have pathogenic mutations for LQT1 or LQT2. Children and adolescents aged 0-18 who were examined in the RCH from January 2004 to December 2014 were evaluated. Patients with known diseases in addition to LQTS that can also contribute to sudden cardiac death or ventricular arrhythmia (including major congenital heart conditions) had been excluded from our analysis. Data regarding demographics, clinical manifestation, electrocardiographic findings, exercise stress test, dosage of beta-blocker used, occurrence of side effects, status at last follow-up assessment, and morbidity and mortality were analyzed. Important treatment modalities including implantation of an implantable cardioverter-defibrillator (ICD) and permanent pacemaker and left cardiac sympathetic denervation (LCSD) were reviewed.

All individuals underwent a Bruce exercise stress treadmill test with continuous ECG recordings during the initial evaluation of their condition, if they were old enough. For the follow-up, a Sprint exercise test was used. The Sprint exercise test consisted of sudden maximal exertion until exhaustion. The acceleration of workload was controlled by cardiologists. The stress test protocol included a 10-min recovery period for the Bruce protocol and 8-min recovery period for the Sprint exercise test.

ECGs at presentation or earliest available ECGs, together with ECGs at exercise tests, were retrieved and analyzed. Measurements were made by a single observer (KSY). QT and the preceding RR intervals were measured in lead II. (If there were no good signals in lead II, then lead V5/V6 would be used.) Measurements were made manually under a magnification adjacent to a scale with 20-ms segments by the tangent method from the beginning of the earliest onset of the QRS complex to the end of the T wave. The QT interval was documented to the nearest 5 ms. The end of T wave was defined as the intersection of a tangent from the steepest slope of the last limb of the T wave and the baseline. (Define Q-Q line as baseline.) Four consecutive QT intervals and their corresponding preceding RR intervals were measured. For QTc interval calculation, 4 individual QTc intervals were calculated and then averaged. When sinus arrhythmia was present, we chose 4 consecutive QRS complexes that included the shortest RR interval on the page. The QT interval measurements were corrected for heart rate using the Bazett correction formula (QTc = QT/√RR). ECGs at baseline, 2 min, 3 min, 5 min, and 8 min into the recovery phase of exercises were analyzed. Z-scores at 2 min, 3 min, 5 min, and 8 min were obtained using the normative data presented by Berger et al. [5].

Genetic mutations of the KCNQ1 amino acid sequence were characterized by membrane spanning, C-loop, N-terminus, and C-terminus as outlined by Barsheshet et al. [6]. The transmembrane region was defined as the coding sequence involving amino acid residues from 120 through 355 [7]. The membrane-spanning region was defined as the coding sequence involving amino acid residues between 124 and 170 (S1–S2), 196 and 241 (S3–S4), and 263 and 355 (S5–S6). The C-loop regions were defined by residues 171–195 (S2–S3) and 242–262 (S4–S5). The N-terminus region was defined before residue 124, and the C-terminus region after residue 355. The pore region of the KCNQ1 channel was defined as the area extending from S5 to the midpoint of S6 involving amino acid residues 301 through 320.

2.2. Statistical analysis

All analyses were performed with the SPSS. Categorical variables were expressed as the number of patients and percentage, and continuous variables were expressed as mean or median ± SD. Statistical significance was set at \( p \leq 0.05 \). Continuous variables were assessed by using one-way analysis of variance, with post-hoc analysis with the Tukey test, and a two-tailed Student t-test. Differences in the categorical variables were assessed using the Pearson chi-square test. Z-scores at different minutes into the recovery phase of exercise were compared using an independent t-test.

2.3. Reliability

Twenty randomly selected ECGs in the cohort were chosen. KSY and JM, being blinded to patient identity and masked to the previous measurements, measured the QTc intervals independently according to the methodology. The interobserver reliability was analyzed. The reliability was assessed by the limit of agreement method of Bland and Altman.

3. Results

3.1. Patient characteristics and long-term follow-up

A total of 86 genetically proven LQT1 and LQT2 patients (50 boys and 36 girls) were identified (44 families). There were 67 LQT1 and 19 LQT2 patients. Among the 86 patients, 20 patients were not under our active follow-up, 14 patients of which were referred out due to adult transition or geographical reasons while 6 patients were lost to active follow-up. However, no death was noted or reported. The median age of diagnosis was 37.5 months (0–209), and the median follow-up period was 4.29 years (0.1–17.3). Their mean QTc intervals are shown in Fig. 1a and b. Proband had significant longer QTc...
The QTc intervals, heart rates, and Z-scores of QTc intervals (mean ± SD) of LQTS subjects at different minutes into the recovery phase of exercise.

| Minutes into the recovery phase of exercise | QTc interval (s) | Heart rate (bpm) | Z-score (QTc) |
|--------------------------------------------|-----------------|-----------------|--------------|
| 2 min                                      | 0.471 ± 0.037   | 109.6 ± 15.4    | 2.12 ± 1.99  |
|                                            | (0.397–0.546)   | (83.3–150.0)    | (−1.82–6.07) |
| 3 min                                      | 0.473 ± 0.037   | 104.3 ± 13.3    | 1.78 ± 2.10  |
|                                            | (0.412–0.566)   | (83.6–130.2)    | (−1.59–6.94) |
| 5 min                                      | 0.469 ± 0.036   | 107.1 ± 10.7    | 1.09 ± 1.91  |
|                                            | (0.398–0.586)   | (78.4–125.0)    | (−2.65–7.25) |
| 8 min                                      | 0.461 ± 0.028   | 99.9 ± 10.0     | 0.95 ± 1.54  |
|                                            | (0.403–0.531)   | (80.4–119.0)    | (−2.27–4.84) |

There was a total of six patients who received LCSD in our cohort. Five out of six patients were offered LCSD because of poor medication compliance as described. Another consideration in one of these five patients was the need for co-administration of psychotropic medication. One out of six patients was offered LCSD because of a significantly prolonged QT interval with syncope despite beta-blocker therapy.

3.2. Exercise test evaluation

Among genetically proven LQT1 and LQT2 patients, only 30 patients had taken exercise tests before the treatment with beta-blocker. All other patients either were too young to undergo an exercise test or had started treatment before an exercise test. One patient record could not be retrieved.

For the 29 patients analyzed (LQT1:LQT2 = 24:5), the median age was 9.7 ± 3.8 years (3.4–14.9). Four patients were probands, and the rest were SFM. The mean QTc intervals at rest before an exercise test was 0.442 ± 0.046 (0.340–0.550). Table 1 shows the mean QTc intervals, heart rates, and Z-scores of QTc intervals at 2 min, 3 min, 5 min, and 8 min into the recovery phase of exercise. The Z-scores were compared using the independent t-test, and the result is shown in Fig. 2. The Z-scores of QTc intervals decreased with increasing minutes into the recovery phase of exercise. The QTc intervals at 2 min and 3 min were statistically significantly longer than those at 5 min and 8 min into the recovery phase of exercise.

Subgroup analyses of LQT1 and LQT2 patients are shown in Fig. 3a and b, respectively. Subgroup analysis for LQT1 patients demonstrated similar results, with the QTc intervals at 2 min and 3 min significantly longer than those at 5 and 8 min into the
recovery phase of exercise. However, for LQT2 patients, no significant difference in QTc interval Z-scores was found at different minutes into the recovery phase of exercise. QTc interval Z-scores of LQT1 patients with different mutation sites were also compared. No significant difference in QTc interval Z-scores was found across different mutation sites except for transmembrane mutation versus C-terminus in LQT1 patients (Fig. 4). The QTc interval Z-scores of LQT1 patients with transmembrane mutation were longer than those with C-terminus mutation at 2 min, 3 min, and 5 min into the recovery phase of exercise. The difference reached statistical significance only at 3 min \( (p = 0.029) \).

3.3. Reliability of results

The Bland–Altman comparison was used to compare QTc intervals calculated by KSY and JM. Bland-Altman limits of agreement (reference range for difference) was \(-0.002 \) to 0.012, that is, in 95% of the time, the 2 measurements were within 0.01 \( \pm \) 0.012, that is, 0.022 of each other. Their mean difference was 0.0011 (95% confidence interval: 0.00154–0.00374).

4. Discussion

LQTS is an inherited cardiac arrhythmia disorder manifesting with syncope, ventricular arrhythmias, and sudden cardiac death. LQT1 and LQT2 are the most common subtypes of LQTS (40–55% and 35–45% of the cases, respectively) [8–10]. We aim to report our center’s experience in the management of LQT1 and LQT2 in children and adolescents over the past 10 years. Atenolol use in pediatric LQTS and routine use of an exercise test in LQTS patients are part of our routine management. With reference to the latest diagnostic guideline by the European Society of Cardiology [11], LQTS could be diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration. Therefore, all genetically proven LQT1 and LQT2 patients and SFM were included.

4.1. Atenolol in pediatric LQTS

Recent genetic advances have led to evolutionary changes in the understanding of the pathophysiology, clinical manifestations, prognosis, and specific therapy of the condition. Beta-blocker is recognized as the efficacious mainstay of therapy for LQT1 and LQT2. Atenolol is a common beta-blocker used in children in the Asia-Pacific region, in contrast to other parts of the world [12]. In Australia, atenolol has been used as the first-line choice of beta-blocker for children and adolescents with LQTS due to its availability. In our institution, atenolol is also available in a mixture form, and it has been given as an alternative to propranolol in infants. With its longer half-life than propranolol and associated good compliance, atenolol became our first choice of beta-blocker over the past years.

Beta-blockers are an effective medication in preventing cardiac events and ventricular arrhythmia, especially in patients with LQT1 and LQT2 [13]. Many LQTS registries have described the results of different types of beta-blockers in the management of patients with LQTS, yet prospective studies comparing the efficacy of different beta-blockers have not been performed. Therefore, controversy exists regarding the efficacy of cardioselective beta-blockers such as atenolol [14]. One previous study even showed up to 60% failure rate of atenolol [15]. A recent study on 382 LQT1 and LQT2 patients, by Chockalingam et al., comparing the use of propranolol, metoprolol, and nadolol, suggested that symptomatic patients on metoprolol had a higher rate of recurrence of cardiac events. For asymptomatic cohort, the prophylactic efficacy of the three beta-blockers was the same for both LQT1 and LQT2 (<1 year of age was excluded) [16]. With atenolol sharing the same cardioselective property as metoprolol, its therapeutic efficacy was challenged. However, atenolol was not directly studied.

The use of atenolol was, however, supported by some other previous studies. One study of 971 LQT1 and LQT2 patients from the International LQTS Registry investigated the efficacy of beta-blockers in reducing the risk of cardiac events. Among LQT1 patients, atenolol showed the greatest efficacy out of the different beta-blockers in reducing cardiac event rates (HR 0.23, \( p = 0.008 \)) whereas metoprolol exhibited the lowest efficacy (HR 0.65, \( p = 0.7 \)). Among LQT2 patients, nadolol was the most effective beta-blocker (HR 0.13, \( p = 0.01 \)) whereas atenolol was not associated with a
significant reduction in cardiac event rates (HR 0.69, p = 0.34) [17]. No subgroup analysis of treatment efficacy on the pediatric age group was provided though. The recent largest registry of 1530 LQTS patients, regarding the use of propranolol, atenolol, metoprolol, and nadolol, was published in 2014 [18]. In the overall cohort, all beta-blockers seemed equally effective in reducing the risk of a first cardiac event. For LQT1 cohort (n = 379), no single type of beta-blocker was found superior to one another in preventing first cardiac events, though nadolol was found to be superior in LQT2 (n = 406). In high-risk patients, propranolol was even found to be inferior to its counterparts, though this may be explained by the use of propranolol in high-risk infants.

Another retrospective observational study regarding the use of atenolol in children was conducted in Texas and Argentina with 57 patients in two centers, with a follow-up period of 5.4 ± 4.5 years. Only one patient died due to noncompliance to medication. Four patients suffered from ventricular arrhythmia, and three patients changed to another beta-blocker due to various reasons. The author concluded that atenolol is a valid and effective therapeutic option for LQTs. However, no genetic information of the patients was provided in this study. Therefore, the therapeutic effects on each subclass of LQTS cannot be evaluated [19].

Concerning its side effects, atenolol seemed to be well tolerated in our study, even at higher doses, with only one patient experiencing intolerable side effects and requiring a change to nadolol for continuation of therapy. However, this contrasted with the number of patients who experienced side effects secondary to atenolol in the study by Trippel and Gillette [15], who reported an incidence of cardiovascular side effects in 4 of 20 patients and non-cardiovascular side effects in 9 patients. Moreover, in their group of patients, atenolol had to be discontinued for 10% of the patients. In fact, previous studies that showed inferiority of atenolol included patients who took atenolol on a once-a-day dose. It is unclear how a once-a-day dose instead of twice a day is contributing to the lack of efficacy in these studies.

A single-pediatric-center experience on the use of atenolol for children and adolescents with LQTS is scarce. This study demonstrated atenolol can be an effective beta-blocker in children and adolescents if compliance is good. Only one LQT1 proband with a QTc interval of 0.6 s in our cohort had developed ventricular arrhythmias on atenolol use. In addition, it proved atenolol was well tolerated in almost all of our patients, with minimal side effects. Our success in atenolol therapy was likely related to our twice-daily regimen in most of our patients and the use of an exercise test and Holter examinations to assess the degree of beta-blockade. Cascade clinical and genetic screening of family members in Australia explains why our cohort has a very large proportion of asymptomatic SFM (84%), which might be another contributing factor to our low cardiac event rates.

So far, there is no strong evidence of the superiority of one beta-blocker in patients with LQT1, so we do not see a need to change our practice of using atenolol in our children with asymptomatic LQTS, especially LQT1 patients. In symptomatic patients with LQT1 and LQT2, many would consider the prescription of nadolol; however, it is not routinely available in Australia.

4.2. Exercise evaluation

It is now recognized that up to 30% of gene-positive individuals may have a normal QTc interval at rest (phenotype negative) [20,21]. In patients with borderline QTc intervals, LQTS may be unmasked by provocative maneuvers. The behavior of QT and QTc intervals during the recovery phase of an exercise test has been proposed as a means of diagnosing LQTS [8,22,23]. Therefore, for the scoring system as the diagnostic criteria for LQTS, the QTc interval prolongation at the recovery phase after an exercise stress test was added in 2011. In the study conducted by Sy et al. [24] in 69 relatives of genotyped LQT1 or LQT2 patients, they found that the combination of resting QTc interval with QTc interval at 4-min recovery phase could predict positive genetic results. The recovery phase of the test was also proved to enhance the diagnostic accuracy in LQT1 and LQT2 patients [25]. Recently, Horner et al. analyzed 243 patients (82 LQT1, 55 LQT2, 18 LQT3, and 88 genotype-negative cases regarded as normal) using an exercise stress test and observed that a paradoxical increase in QTc interval during the recovery phase distinguishes LQTS patients, particularly LQT1, from controls and found that LQT2 patients also lengthen their QTc interval from the third minute of recovery [26].

In our study, when comparing our genetically proven patients with the normal reference we previously published, we can still observe the overlapping region previously mentioned. For LQT1 patients, QTc interval prolongation at 2–3 min into the recovery phase of exercise was more prominent than the prolongation in the later part of the recovery phase of exercise. This difference was not observed in LQT2 patients.

Mutations in the transmembrane region of the KCNQ1 potassium channel have been shown in previous studies to put patients at higher risk of cardiac events. The QTc interval was longer and has been associated with greater sensitivity to sympathetic stimulation as determined by the effect of exercise treadmill test on the QTc interval. Exaggerated QTc interval prolongation with exercise has been demonstrated in patients with transmembrane mutation sites [27,28]. Lakman et al. tried to reproduce similar findings in comparing 1-min and 4-min recovery QTc intervals in their cohort with transmembrane versus non-transmembrane mutations. However, no significant difference could be demonstrated [29]. In our subgroup analysis, we could show that QTc intervals in patients with transmembrane mutation were longer than their C-terminus counterparts. The difference was statistically significant at 3 min into the recovery phase of exercise.

Among the mutations studied in previous literature, the presence of C-loop mutations was associated with the longest QTc interval on the ECG and with highest risk for ACA or SCD [6]. However, there were only 3 patients with C-loop mutation, and only 1 of them was old enough to undergo an exercise test. Therefore, no meaningful comparison could be performed for C-loop mutation.

4.3. Limitation

Using data from an observational study might be biased through the selection of patients seen in a tertiary center, and retrospective data collection is not always complete. Only patients with genetically proven LQT1 and LQT2 are included in our cohort. Measurement of QTc interval is difficult, especially during and after an exercise test. Recalculation was performed again instead of a chart record only to ensure that accurate QTc intervals were represented. We tried to test the reliability because of a single-observer calculation, but the reliability test demonstrated no significant interobserver variability, with our well-defined methodology.

Additionally, the evaluation of an exercise test only included patients who have undergone a treadmill exercise test before beta-blocker therapy. Some LQTS patients were not included in the analysis owing to them not being physically able to exercise for they were too young or the beta-blocker had been started before exercise evaluation, both of which could be sources of bias.

Our study is limited in power to investigate inter-mutation site difference because of the small patient cohort. As a retrospective cohort, it is difficult to ascertain whether a maximal exertion was achieved (achievement of VO2 max and anaerobic thresholds),
though patients were always encouraged to exercise until absolute fatigue.

Finally, QTc interval measurements were made using the Bazett correction formula. This formula has wide acceptance and use, but it can overcorrect and undercorrect heart rates greater than 100 bpm and 60 bpm, respectively [30].

5. Conclusion

Atenolol is an effective treatment for genetically proven LQT1 and LQT2 children and adolescents, with good tolerability. There was no arrhythmic death reported in our cohort on atenolol treatment. In LQT1 patients, QTc intervals at 2–3 min into the recovery phase of exercise were significantly prolonged, particularly in patients with transmembrane mutations.

Conflict of Interest

All authors declare no conflict of interest related to this study.

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