Predictive factors for an effective beta-blocker therapy in Chinese patients with congenital long QT syndrome: A multivariate regression analysis

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OBJECTIVE: To investigate the factors that may predict the effectiveness of beta-blocker therapy for congenital long QT syndrome (LQTS) in a Chinese patient population.

METHODS: Twenty-six LQTS patients were treated with oral propranolol (n=16) or metoprolol tartrate (n=10) for 38 months. Clinical symptoms, heart rate, corrected QT interval (QTc) and left ventricular ejection fraction were assessed before and after the therapy.

RESULTS: Cardiac events were reduced by more than 50% in 22 patients with beta-blocker therapy. The average number of syncopes/patient and the average frequency of syncopes/patient/year in the responders were reduced from 16.2±5.1 to 1.1±0.9 (P<0.01) and from 4.5±1.2 to 0.7±0.6 (P<0.01), respectively. The QTc was also reduced from 0.56±0.06 s to 0.50±0.03 s. There was no significant difference in the reduction of syncopies and QTc in patients treated with propranolol and metoprolol tartrate. Multivariate regression analysis showed no correlation between the reduction in syncopal attacks and patients’ age, sex, heart rate or left ventricular function (P>0.05). QTc reduction was the only independent predictive factor for syncope control (R=0.81, P<0.001).

CONCLUSIONS: Oral beta-blockers are an effective therapy for Chinese patients with LQTS. A significant reduction in QTc is highly indicative of treatment success with beta-blockers.

Key Words: Beta-blockers; Cardiac electrophysiology; ECG; Long QT syndrome; QT interval; Tachycardia

PATIENTS AND METHODS

Patients
Detailed clinical data including present and past medical history, physical examination, biochemistry profile and ECG were obtained from 26 Chinese patients (nine males and 17 females) who were diagnosed with LQTS according to the Schwartz criteria (7). The average age of the patients was 19±10 years (range two to 46 years). All patients had a prolonged QTc on ECG, and frequent syncopal attacks ranged from three times/year to 10 times/year, for an average of 6.8±2.9 years (range 1.5 to 11 years) before the study. The most common triggers of the cardiac events were physical exercise, sporting activities or emotional stress.

Physical examination, a chest x-ray, and two-dimensional and Doppler echocardiography showed no structural heart disease in these patients.

No genetic studies were performed to subtype the patients. However, the ST-T morphologies on 12-lead ECG were consistent with those found in LQT1 or LQT2 subtypes (8).

Antiadrenergic therapies and follow-up
All patients were treated with either propranolol or metoprolol tartrate (Table 1). No other medications were administered in these patients at the time of the study. The dosage of the beta-blockers was increased from a smaller initial dose to the maximum tolerable dose in four to six weeks. Patients were followed-up initially on a

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The QT interval was measured from lead II on body surface ECG. The QTc was calculated using Bazett's formula (QTc=QT/RR1/2) and reported in milliseconds. In each patient, QTc was the average QTc before therapy, baseline heart rate, left ventricular ejection fraction, and age, sex, history of the disease, frequency of syncopal attacks before therapy, baseline QTc, type of beta-blocker and the QTc reduction after therapy (P>0.05, Table 2). There was no mortality during the six-year follow-up period.

In the four patients who did not respond to beta-blocker therapy, the average QTc before and after therapy was 550±40 ms and 560±70 ms, respectively (P>0.05).

Predictive factors for successful beta-blocker therapy
A multivariate regression analysis showed that treatment success of beta-blockers had no correlation with patients' age, sex, history of the disease, frequency of syncopal attacks before therapy, baseline heart rate, baseline left ventricular ejection fraction, baseline QTc and the type of beta-blocker used for the treatment (P>0.05). However, there was a significant correlation between the QTc reduction and treatment success (R=0.81, P<0.001).

In the present study, more than 80% of the patients responded to beta-blocker therapy, resulting in a significant reduction in the frequency and total number of syncopal attacks. The average heart rate in the 22 patients was reduced by 14 beats/min (Table 2). In two patients who had a complete prevention of syncope, propranolol induced sinus bradycardia, which was subsequently treated with a permanent pacemaker. They remained symptom free during the six-year follow-up period.

Other adverse effects of the beta-blocker therapy included nightmares in five patients, general fatigue in six and cold hands or feet in three patients.

QTc reduction after beta-blocker therapy
Among the 22 patients who responded to beta-blocker therapy, the average QTc was shortened after therapy (P<0.01, Table 2). QTc remained unchanged in two patients, although the average annual frequency of syncope was reduced from six to one syncope/year. There was no significant difference in the average QTc reduction between those treated with propranolol and metoprolol tartrate (600±30 ms versus 600±20 ms, respectively; P>0.05).

The average heart rate in the 22 patients was reduced by 14 beats/min (Table 2). In two patients who had a complete prevention of syncope, propranolol induced sinus bradycardia, which was subsequently treated with a permanent pacemaker. They remained symptom free during the six-year follow-up period.

DISCUSSION
Management of LQTS
The major cause of symptoms and mortality in LQTS is ventricular arrhythmias, such as torsades de pointes or cardiac arrest (1-3). Beta-blockers have been shown to significantly reduce or prevent cardiac events in most LQTS patients (4). If patients continue to have syncope or aborted cardiac arrest despite full-dose beta-blocker therapy, left cardiac sympathetic block will provide symptom relief and a reduction in cardiac death in most patients (5,6). However, when cardiac arrest is the presenting symptom, an implantable cardioverter defibrillator should be used in addition to antiadrenergic therapy (1,9). Other interventions, such as potassium supplements, mexilitine HCl or verapamil HCl, should be considered experimental and reserved for the rare patient who continues to have syncopal episodes despite adequate antiadrenergic therapies (1-3).

In the present study, more than 80% of the patients responded to beta-blocker therapy, resulting in a significant reduction in the frequency and total number of syncopal attacks. The average dose of the beta-blockers used in the present study was slightly lower than previously reported doses, but the suppression in cardiac events was similar (4). Furthermore, there was no significant difference in the treatment success between propranolol- and metoprolol tartrate-treated groups, indicating the type of beta-blocker used was not critical to the clinical outcome in patients with LQTS.
Effect of beta-blockers on QTc

QT intervals on body surface ECG are often used as a clinical measure of the duration of ventricular repolarization. A recent study (4) showed that beta-blockers reduced QTc in patients with LQTS by an average of 20 ms (4). In the present study, QTc remained unchanged in the four patients who failed to respond to beta-blocker therapy. However, in patients who responded to beta-blocker therapy, an average 60 ms QTc reduction was observed. In addition, QTc remained unchanged in two patients with significant symptom relief, suggesting that the clinical effects of beta-blockers involved a more complex mechanism in these patients.

Predictive factors of successful beta-blocker therapy

The prevalence of LQTS appears to be correlated with age and sex; children and women are more likely to be affected by the disease than adults and men (1-3,10). It is not clear whether age and sex are correlated with the therapeutic responses to beta-blocker therapy. A recent study (11) found that adult male patients with the LQT1 subtype experienced the most significant reduction in QTc and improvement in cardiac events after beta-blocker therapy. Multivariate regression analysis in the present study, however, failed to show any significant correlation between syncope reduction and age or sex. The type of beta-blocker, heart rate and the left ventricular systolic function before therapy also had no relationship with the reduction in syncopal attacks. The only independent predictive factor for a positive response to beta-blocker therapy was a shortening of QTc.

Limitation of the study

The major limitation of the present study was that the number of patients included was relatively small, and the follow-up period was relatively short compared with previous studies, such as the international registry by Moss et al (4). However, our results were generally consistent with those of the international registry, which was largely comprised of heterogenetic patients with different ethnic backgrounds (1,4), indicating that Chinese patients respond to beta-blocker therapy in a similar fashion.

It is interesting to note that the average QTc shortening during beta-blocker therapy was 60 ms, which was greater than the 20 ms shortening reported in a larger scale study (4). Whether this difference in QTc reduction was due to the difference in patient numbers, patient selection bias or other factors, such as ethnic background, is unclear.

CONCLUSIONS

The data in the present study show that oral beta-blockers are highly effective in the management of Chinese patients with LQTS. The clinical outcomes of beta-blocker therapy were age- and sex-independent, but were closely related to a reduction in syncopal attacks. The only independent predictive factor for a positive response to beta-blocker therapy was a shortening of QTc.

REFERENCES