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

Lexin Wang MD PhD[1,2], Tongguo Wu MD[1]

L Wang, T Wu. Predictive factors for an effective beta-blocker therapy in Chinese patients with congenital long QT syndrome: A multivariate regression analysis. Exp Clin Cardiol 2004;9(3):193-195.

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 syncopes 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*

Congenital long QT syndrome (LQTS) is a potentially fatal cardiac electrophysiological disorder that mainly affects children and young adults (1-3). The main clinical manifestations of LQTS are episodic syncopal or presyncopal attacks and a prolongation of the corrected QT interval (QTc) on body surface electrocardiography (ECG) (1-3). The pathogenesis of LQTS has been under intensive investigation in recent years. It is has been suggested that mutations of the genes that encode ventricular cell membrane potassium or sodium channels are the main cause of LQTS (1-3). Ion channel dysfunction leads to a prolongation in ventricular repolarization, QTc prolongation on body surface ECG and ventricular arrhythmias, such as torsades de pointes or cardiac arrest (1-3).

Sympathetic activity is believed to play a critical role in the induction of QTc prolongation and torsades de pointes in patients with LQTS (1-3). For this reason, antiadrenergic therapies with either oral beta-blockers or left cardiac sympathectomy have been the mainstay of treatments that reduce the frequency of cardiac events or sudden cardiac death in up to 70% of these patients (4-6). Although beta-blockers are highly effective in reducing or preventing cardiac events in LQTS, up to 30% of patients still experience syncope or aborted cardiac arrests during the course of therapy (4). The primary purpose of the present study was to investigate the clinical characteristics that may predict the clinical outcomes of beta-blocker therapy in a Chinese patient population.

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

[1]*Department of Cardiology, The Affiliated Hospital of Taishan Medical College, Taishan City, People's Republic of China;* [2]*School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, New South Wales, Australia*
Correspondence: Dr Lexin Wang, School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, New South Wales 2678, Australia. Telephone 61-2-6933-2909, fax 61-2-6933-258, e-mail lwang@csu.edu.au

TABLE 1
The dosage regimens of beta-blockers

Drug	Initial average dose, mg/day (range)	Final average dose, mg/day (range)
Propranolol (n=16)	35.5±10.5 (20–60)	67.5±39.1 (30–120)
Metoprolol tartrate (n=10)	20.8±2.5 (25–50)	60.0±5.5 (50–100)

TABLE 2
The characteristics of patients who responded to beta-blockers

Parameter	Before beta-blocker therapy (n=22)	After beta-blocker therapy (n=22)	P
Total number of syncopes/patient	16.2±5.1	1.1±0.9	<0.01
Number of syncopes/patient/year	4.5±1.6	0.7±0.6	<0.01
Heart rate (beats/min)	81±7	67±5	<0.01
QTc (ms)	560±60	500±30	<0.01
LVEF (%)	65±6	66±9	NS

LVEF Left ventricular ejection fraction; NS Not significant; QTc Corrected QT interval

bimonthly basis, with a full physical examination and 12-lead ECG performed during each clinic visit. Once the dosage and clinical symptoms were stabilized, the follow-up was performed every six months. Two-dimensional and Doppler echocardiography were performed before and at the end of the study to assess left ventricular function.

Effective therapy was defined as a more than 50% reduction in the frequency of annual syncopal attacks.

Measurement of QTc

The QT interval was measured from lead II on body surface ECG. The QTc was calculated using Bazett's formula ($QTc=QT/RR^{1/2}$) and reported in milliseconds. In each patient, QTc was the average value from three consecutive cardiac cycles.

Statistics

Data were expressed as mean ± SD. The differences in QTc before and after therapy were analyzed with ANOVA. Percentage data were analyzed using the χ^2 test. A multivariate regression analysis was used to evaluate the relationship between treatment success and age, sex, history of the disease, frequency of syncopal attacks before therapy, baseline heart rate, left ventricular ejection fraction, baseline QTc, type of beta-blocker and the QTc reduction after therapy. $P<0.05$ was considered statistically significant.

RESULTS

Clinical effects of beta-blockers

After an average of 38±12 months (median 36 months, range 32 to 336 months) follow-up, a significant reduction in the total number of syncopal attacks was observed in 22 patients (84.6%) ($P<0.01$, Table 2). The frequency of the annual syncopal attacks was also reduced ($P<0.01$, Table 2). In seven patients, syncope was completely prevented during the follow-up period. There was no significant difference in the success rate between the propranolol and metoprolol tartrate groups (81% versus 90%, respectively; $P>0.05$).

The left ventricular ejection fraction remained unchanged after therapy ($P>0.05$, Table 2). There was no mortality during the follow-up period.

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; $P>0.05$).

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, 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 ($R=0.81$, $P<0.001$).

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 sympathectomy 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 are 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 QTc.

REFERENCES

1. Schwartz PJ, Priori SG, Napolitano C. The long QT syndrome. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology: From Cell to Bedside. Philadelphia: WB Saunders, 2000:597-610.
2. Khan IA. Long QT syndrome: Diagnosis and management. Am Heart J 2002;143:7-14.
3. Wang L. Congenital long QT syndrome: 50 years of electrophysiological research from cell to bedside. Acta Cardiol 2003;58:133-8.
4. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000;101:616-23.
5. Schwartz PJ, Locati EH, Moss AJ, Crampton RS, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. A worldwide report. Circulation 1991;84:503-11.
6. Li J, Wang L, Wang J. Video-assisted thoracoscopic sympathectomy for congenital long QT syndromes. Pacing Clin Electrophysiol 2003;26:870-3.
7. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: An update. Circulation 1993;88:782-4.
8. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation 2000;102:2849-55.
9. Welde AA. Is there a role for implantable cardioverter defibrillators in long QT syndrome? J Cardiovasc Electrophysiol 2002;13:S110-3.
10. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long QT syndrome: Findings from the International LQTS Registry. Circulation 1998;97:2237-44.
11. Conrath CE, Wilde AA, Jongbloed RJ, et al. Gender differences in the long QT syndrome: Effects of beta-adrenoceptor blockade. Cardiovasc Res 2002;53:770-6.