CARDIAC SAFETY

Role of Bisoprolol in Patients with Long QT Syndrome

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Background: Long QT syndrome (LQTS) is a disorder of ventricular repolarization usually treated with β-blockers, mostly with propanolol and nadolol. The aim of our study was to evaluate the role of bisoprolol in LQTS patients.

Methods: A total of 34 patients were evaluated in an average follow-up time of 93 months: 31 months without treatment, 31 months in treatment with nadolol or propanolol and 31 months in treatment with bisoprolol. The average age of patients at diagnosis was 17.3 years. The enrolled patients were followed through a semiannual electrocardiogram and an annual 24-hour Holter monitoring. All patients underwent genotyping, routine hematologic tests, and an echocardiogram.

Results: In 93 months there were 2 major and 12 minor cardiovascular events. Both the major events occurred in absence of β-blocking therapy. Of the 12 minor cardiovascular events 3 occurred in absence of treatment, 7 during treatment with nadolol or propranolol, and 2 during treatment with bisoprolol. The mean heart rate at 24 h Holter was 87 bpm without treatment, 71 bpm in patients treated with propanolol and nadolol, and 70 bpm in patients treated with bisoprolol. There were not statistically significant differences between the three groups in the mean QTc.

Conclusions: Beta-blocking therapy is the cornerstone of LQTS therapy but actually there is no clear indication about which beta-blocker should be used. In our experience bisoprolol proved to be less harmful and easier to manage than propranolol and nadolol in patients with LQTS, with the same effectiveness in preventing major cardiovascular events.

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INTRODUCTION

Long QT syndrome (LQTS) is a disorder of ventricular repolarization that may lead to torsade de pointes, ventricular fibrillation and therefore, sudden cardiac death.[1–4] A QT interval greater than 440 ms is considered prolonged,[5,6] but generally arrhythmias occur with values of 500 ms or more.

ACC/AHA/ESC 2006 Guidelines[7] recommend the use of beta-blockers in LQTS patients in class I, as level of evidence B but do not indicate which of the beta-blockers should be used in these patients. The most widely prescribed beta-blockers in LQTS are propanolol and nadolol. Propanolol is a non-cardioselective beta-blocker, which requires, having a short half-life, multiple daily doses. Nadolol was withdrawn from the market in Italy in 2008. In our study, we evaluated the effect of bisoprolol, a high cardioselective beta blocker that requires just one daily dose, in LQTS patients.

MATERIALS AND METHODS

A total of 34 patients, 17 probands and 17 family members, were evaluated in an average follow-up time of about 7.8 years, for a total of 93 months. The average age of patients at diagnosis was 17.29±15.52 years, range 1–51. The average age at the end of the follow-up period was 25.05±15.53 years, range 9–59 years. The median at the end of the follow-up period was 20 years. In all these patients an ECG (Cardioline Delta 3 plus, Remco

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Table 1. Characteristics of the Patients Enrolled in the Study

Patients	34
Mean follow-up time (years)	7.8
Mean age at diagnosis (years)	17.3
Mean age at the end of follow-up (years)	25.05
Median at the end of follow up (years)	20

Italia Spa, Vignate, Italy) showed a prolonged QTc of 450 ms or more. And 4 patients underwent an ECG because of clinical symptoms, while the other patients underwent and ECG because of familiarity for LQTS or other reasons (see Table 1).

The enrolled patients were followed in our cardiology division through a semiannual electrocardiogram and annual 24-hour Holter monitoring (SpiderView, ELA Medical, Le Plessis-Robinson Cedex, France). All patients underwent routine hematologic tests and an echocardiogram and no abnormalities were recorded. A genotyping was done evaluating the main genes implicated in LQT1, LQT2 and LQT3 in all patients in an Italian referral center for molecular cardiology: it revealed LQT1 in 9 patients, LQT2 in 2 patients and no LQT3. In the remaining 23 patients no genetic mutation was found.

A Microsoft Word software (Redmond, WA, USA) record card was created for all patients, as is routinely done in our department. Data were stored in our server and held throughout the observation period.

Data were collected in a Excel database (Microsoft), statistical analyses were done through stat view and graphics were created using power point.

All patients enrolled were asked to sign a consent form to use their personal data in accordance with the dispositions foreseen by the law 675/96, and every patient also had to read an informative report about the tutelage of the personal data, according to the same law. Statistical analyses were done after removing personal data according to the forementioned law.

The present project is an observational study and so it is not subject to the directive 2001/20/CE of the European Parliament regulating the application of a good clinical practice during clinical experimentation (Art. 1 comma 1; Art 2/c) and so it was not necessary to obtain an Ethics Committee ruling.

RESULTS

In an open study on 34 patients, 3 periods of treatment per patient were evaluated: no treatment before diagnosis, treatment with nadolol or propanolol (1–3 mg/kg) started at diagnosis and treatment with bisoprolol (0.1–0.2 mg/kg) in the third period.

A total of 93 months were evaluated: 31 without treatment, 31 in treatment with nadolol or propanolol and 31 in treatment with bisoprolol.

The analysis of the events was conducted retrospectively at the end of the follow-up period.

In 93 months, a total of 2 major cardiovascular events (arrhythmic syncopes) were reported (before the diagnosis of LQTS), both resuscitated by electrical defibrillation, and both occurred in absence of beta-blocker therapy. In both patients the event was immediately followed by the diagnosis of LQTS. Both patients had a QTc interval prolongation greater than 500 ms. During beta-blocking therapy, of any type, no episodes of major ventricular arrhythmia were recorded. Moreover 12 nonarrhythmic syncope occurred in 7 patients (2 of them had more than one episode); the arrhytmic origin was excluded after medical history evaluation. As a matter of fact, in 4 cases the syncope occurred without loss of consciousness, without stress and at rest, after exposure to a hot and crowded place and few days after the beginning of beta-blocking therapy. In the remaining 8 cases syncope occurred with loss of consciousness. In 4 cases the syncope was preceded by malaise and blurred vision, and in three of 4 cases a reduction of blood pressure was found. The remaining three episodes occurred in patients in whom vasovagal syncope had been already diagnosed and whose QTc never exceeded 475 ms. Only on one occasion did a loss of sphincter tone occurr, as a result of emotional stress, but a doctor's swift response ruled out the arrhythmic origin.

Of the 12 minor cardiovascular events 3 episodes occurred in absence of treatment, 7 during treatment with nadolol or propranolol (2 with nadolol and 5 with propranolol), and 2 during treatment with bisoprolol.

The number of major and minor events occurred and the number of patients with major and minor cardiovascular events in the three periods are reported in Table 2.

All patients underwent annual 24-hour Holter. The average heart rate (HR) was assessed using

Table 2. Number of Major and Minor Events Occurred and Number of Patients with Major and Minor Cardiovascular Events

	No Treatment	Nadolol or Propanolol	Bisoprolol
Number of major events	2	0	0
Number of patients with major cardiovascular event	2	0	0
Number of minor events	3	7	2
Number of patients with minor cardiovascular event	3	6	1

Table 3. Results on HR and Qtc at 24h-ECG Holter

	No Treatment	Nadolol or Propanolol	Bisoprolol
HR	87 (71–91)	71 (61–86)	70 (61–88)
QTc (ms)	470	469	468

HR = heart rate; QTc = corrected QT interval.

three 24-hour Holter recordings: the first Holter was performed during the period without any treatment or within 24 h after beginning of therapy, the second during treatment with propanolol or nadolol and the third during treatment with bisoprolol: the average HR was 87 bpm (range 71–91 bpm) on the first Holter monitoring, 71 bpm (range 61–86 bmp) on the second, and 70 bpm (range 61–88 bpm) on the third.

There were not statistically significant differences between the three groups in the average QTc calculated as an average of 7 gathered values in the Holter performed each year (sum of all values obtained).

Results on HR and QTc are showed in Table 3.

DISCUSSION

LQTS is a rare arrhythmic syndrome which can lead to sudden cardiac death.[3,4] Beta-blocking therapy is nowadays the cornerstone of LQTS therapy and it's recommended in class I, as level of evidence B in these patients.[7] Most LQTS patients can be managed effectively with these drugs, but around 20% do not respond.[8,9] Moreover patients with LQT1 and in particular those with some specific mutations gain a greater benefit when treated with beta-blockers compared to patients having other mutations independent of clinical risk factors.[10,11]

However the guidelines do not indicate which beta-blocker should be used in these patients. In scientific literature propranolol and nadolol are most commonly used for the treatment of this syndrome.[12,13] Propranolol is a noncardioselective beta-blocker with a short half-life that requires more daily doses (3 is recommended), and in our experience often leads to important hypotensive effects.

Nadolol is a cardioselective beta-blocker, tested in children, with a specific indication on the data sheet for the treatment of long QT syndrome. However, for economic reasons, in Italy, there has been difficulty in obtaining this drug and today it is available only after activation of complicated bureaucratic procedures. The drug is administered once per day and on the market it only exists in the dose of 80 mg.

Bisoprolol is the most commonly used beta-blocker in Italy in coronary artery disease. It is the most cardioselective beta-blocker on the market at the moment, with the greatest affinity for the beta1 receptors and the lowest one for the beta 2 alpha1 receptors. There are many commercially available doses, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 6.25 mg, 7.5 mg, 8.75 mg and 10 mg.

LQTS is a genetic disease usually diagnosed in childhood period and during adolescence. In this age when body weight is increasing, drug administration is often pro kg of body weight and grows over time.

In our department many patients with ischemic heart disease are followed and bisoprolol is routinely used. Due to the difficulties in finding nadolol and to difficulties in propanolol administration we chose to begin therapy with bisoprolol in patients with long QT syndrome. As shown in the results listed before, bisoprolol proved to be as effective as propranolol and nadolol in preventing major cardiovascular events in patients with long QT.

As regards syncopes due to orthostatic hypotension, this drug proved to be less harmful, with an incidence of events per month less than

50% compared to other beta-blockers analyzed. The average heart rate at Holter also confirmed the effectiveness of beta-blocker. There was no significant shortening of the QTc interval with any of the beta-blockers as required by the guidelines.

Moreover, the presence in the market of various dosages allowed us to avoid galenic preparations or home prepared complex solutions at increasing doses, as it is usually used in pediatric patients, with better family compliance and greater adherence to therapy of adolescent patients.

CONCLUSIONS

LQTS is a syndrome that may lead to minor and major cardiovascular events and to sudden cardiac death. This syndrome must be treated, in accordance with the guidelines, with beta-blockers and, although there is no clear indication on which beta-blocker should be used, it is generally treated with propranolol or nadolol. In our experience the use of bisoprolol in patients with LQTS has proved to be less harmful and easier to manage than propranolol and nadolol, with the same effectiveness in preventing major cardiovascular events.

All authors contributed equally to the article.

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