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Risk of Cardiac Events in Patients with Asthma and Long QT Syndrome Treated with β_2 -agonists

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Abstract

The clinical course and risk factors associated with β_2 -agonist therapy for asthma have not been investigated previously in patients with the Long QT Syndrome (LQTS). The risk of a first LQTS-related cardiac event due to β_2 -agonist therapy was examined in 3,287 patients enrolled in the International LQTS Registry with QTc 450msec. The Cox proportional hazards model was used to assess the independent contribution of clinical factors for first cardiac events (syncope, aborted cardiac arrest, or sudden death) from birth through age 40. Time-dependent β_2 -agonist therapy for asthma was associated with an increased risk for cardiac events (hazard ratio (HR) = 2.00, 95% confidence interval 1.26–3.15, $p = 0.003$) after adjustment for relevant covariates including time-dependent β -blocker use, sex, QTc, and history of asthma. This risk was augmented within the first year after the initiation of β_2 -agonist therapy (HR = 3.53; $p = 0.006$). The combined use of β_2 -agonist and anti-inflammatory steroids was associated with an elevated risk for cardiac events (HR = 3.66; $p < 0.01$). β -blocker therapy was associated with a reduction in cardiac events in those using β_2 -agonists (HR = 0.14; $P = 0.05$). In conclusion, β_2 -agonist therapy was associated with an increased risk for cardiac events in asthmatic patients with LQTS, and this risk was diminished in patients receiving β -blockers.

Previous studies have indicated that asthma is associated with an increased risk for cardiac events in patients with the long QT syndrome (LQTS), and this risk is diminished with the

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administration of β -blockers.¹ Asthma is an inflammatory disorder of the airways characterized by reversible bronchi obstruction and sporadic bronchospasm.² One of the current treatments of asthma is the use of β_2 -adrenergic receptor agonists for bronchodilation.³ β_2 -adrenergic receptors predominate in the lungs, and approximately 25% of the β -adrenergic receptors in the heart are of the β_2 type.^{4,5} However, current literature provides minimal information on the effects of inhaled β_2 -agonist treatment for asthma in LQTS. Using the International Long QT Syndrome Registry, we determined the risk associated with inhaled bronchodilator therapy for asthma in LQTS patients and the influence of β -adrenergic blockers on outcome in this LQTS population.

Methods

We studied 6,015 members of 1,275 LQTS families enrolled in the International Long QT Syndrome Registry.⁶ Informed consent was obtained for all patients enrolled in the Registry. At the time of enrollment, a baseline electrocardiogram was obtained and measurements were made for RR, QT, and the Bazett-corrected QTc interval.⁷ From the baseline QTc values, we identified 3,287 patients with QTc \geq 450 msec, a subgroup with a high likelihood of being affected with LQTS. The Registry data included detailed information on the clinical history of patients with LQTS, the age when inhaled bronchodilator therapy was initiated for treatment of asthma, and the onset and offset of specific LQTS therapy including β -blockers as previously reported.⁶ Blood samples were obtained for genetic studies in 1,036 subjects with mutation identification by standard genetic tests.

Asthma therapy was initiated at the discretion of each patient's attending physician. In 101 patients treated with inhaled β_2 -agonist bronchodilators, albuterol, salmeterol, or metaproterenol were utilized in 96% of the administered therapy. In 37 patients treated with inhaled steroid therapy, beclomethasone, triamcinolone, or budesonide were utilized in 95% of the administered therapy.

In 1,622 patients who received β -blocker therapy for LQTS, propranolol, atenolol, nadolol, or metoprolol were utilized in 96% of the administered therapy.

The primary end point was the first occurrence of syncope (defined as the transient loss of consciousness that was sudden in onset and offset), aborted cardiac arrest (requiring external defibrillation during resuscitation), or LQTS-related sudden cardiac death (unexpected sudden death exclusive of a known cause) from birth through age 40 years.^{1,8,9} The probability of cardiac events in patients using β_2 -agonists was compared to those not using β_2 -agonists in the LQTS-affected population.

The Wilcoxon test for continuous variables and the χ^2 or Fisher exact tests for categorical variables were used to compare the clinical characteristics between patients with or without β_2 -agonist treatment among the LQTS affected patients. Graphical display of the time to event before and after starting β -agonist therapy utilized the Mantel-Byar method.¹⁰ The Cox proportional hazards model¹¹ was used to evaluate the significant and independent contribution of time-dependent β -agonist therapy to the occurrence of cardiac events. The interaction of time-dependent β -blocker use with β_2 -agonist use was assessed using the Cox

regression model. The statistical software used to perform the analyses was SAS version 9.1.3 (SAS, Cary, North Carolina). All tests were two-sided, and statistical significance set at 0.05 level.

Results

In the study population of 3,287 affected LQTS patients (QTc = 450 msec), 101 (3.1%) patients utilized β_2 -agonist therapy. The clinical characteristics of the LQTS study population by use or non-use of β_2 -agonist therapy are presented in Table 1. There were significant gender, age at baseline electrocardiogram, baseline QTc, and heart rate differences between the 2 treatment groups. Therapy with β_2 -agonists was associated with a higher frequency of syncope. Over 90% of patients receiving β_2 -agonist therapy were categorized as having a history of asthma. β -blocker use was significantly more frequent in the β_2 -agonist treated patients than in those not receiving β_2 -agonist therapy. The dosages of three different β -blockers prescribed in patients with and without β_2 -agonist therapy are presented in Table 2.

Time-dependent β_2 -agonist therapy was associated with an increase in cardiac events as shown in the Mantel-Byar graph (Fig. 1). The findings from the Cox proportional hazards regression analysis for time to first cardiac event are presented in Table 3. Time-dependent β_2 -agonist use was associated with a 2-fold increased risk for cardiac events after adjustment for relevant covariates including sex, QTc, history of asthma, and time-dependent β -blocker use. Males up to age 13 had an augmented risk compared to females of the same age, but the converse was true after age 13. The risk for LQTS-related cardiac events from time-dependent β_2 agonist therapy was greater in the first year after initiation of therapy (HR = 3.53; 95% CI, 1.44–8.64; $p = 0.006$) than in later years (HR = 1.77; 95% CI, 1.06–2.95; $P = 0.03$). In comparing the long-acting versus the short-acting β_2 -agonist therapy, there was no significant difference on the outcome of cardiac events.

Anti-inflammatory steroids were not associated with an augmented risk for cardiac events (HR = 1.61; 95% CI, 0.40–6.47; $P = 0.50$). However, the combined use of β_2 -agonist and anti-inflammatory treatment was associated with an elevated risk (HR = 3.66; 95% CI, 1.37–9.81; $P < 0.01$), possibly reflecting more severe underlying bronchial asthma.

The influence of β -blocker use on patients receiving and not receiving β_2 -agonists was evaluated in an interaction model. β -blockers had no evident effect in those not receiving β_2 -agonists (HR = 1.10; 95% CI, 0.88–1.37; $P = 0.41$), but a meaningful reduction in events was evident in those on β_2 -agonists (HR = 0.14; 95% CI, 0.02–1.04; $P = 0.05$), with a bidirectional interaction significant at $p = 0.05$.

Discussion

This study highlights four important issues regarding asthma treatment in LQTS patients. β_2 -agonist therapy was associated with a two-fold increased risk of cardiac events in patients using this medication, with the risk higher within the first year of starting β_2 -agonist treatment than thereafter. The combination of β_2 -agonist and anti-inflammatory steroids was

associated with a higher probability of cardiac events. The utilization of β -blocker therapy in conjunction with β_2 -agonist treatment lowered the risk of cardiac events.

In the last 25 years, there has been an increase in the incidence and prevalence of asthma,¹² and this increased frequency of asthma surely involves patients with LQTS. Management of LQTS patients with asthma is a challenge since β_2 -agonist therapy represents a relative contraindication because of its potential to trigger ventricular tachyarrhythmias in this repolarization disorder.¹³

In a previous report from the LQTS Registry, Rosero, et al. showed that asthma was associated with an increased risk for cardiac events.¹ In the current study, we showed that the risk is largely related to the use of β_2 -agonist therapy, and this therapy is a more potent risk factor than a history of asthma (Table 3).

The currently recommended treatment for patients with LQTS is administration of β -blocker agents. These drugs diminish the risk of cardiac events by decreasing sympathetic stimulation of the heart.¹⁴ On the other hand, β_2 -adrenergic drugs used in the treatment of asthma work in an opposing manner and are predominately aimed at the β_2 -receptors located primarily in the lungs. These drugs, widely used to treat asthma, are associated with an increased likelihood of cardiac events. Even though the β_2 -adrenergic agonists exert a preferential activity on the adrenergic receptors in the lungs, there is also some concurrent stimulation upon the β -receptors located within the heart. This latter stimulation may trigger cardiac arrhythmias in LQTS resulting in the increased cardiac events as observed in the current study with β_2 -agonist anti-asthmatic therapy.

For asthma patients taking both a β -blocker and a β_2 -agonist, there was a significant reduction in the probability of cardiac events. Although β -blockers may exacerbate bronchospastic asthma,¹⁵ this therapy seems to outweigh the negative effect imparted by the β -agonist therapy on cardiac events. While there was an increase in syncope with β_2 -agonist use, we did not identify any fatal cardiac events in patients receiving asthmatic therapy. We cannot exclude the possibility that the ICD that was implanted in 18% of the β_2 -agonist group prevented mortality, but we think this is unlikely for several reasons. Appropriate ICD shocks for life-threatening arrhythmias in LQTS are quite infrequent.¹⁶ When we excluded patients with ICDs from the Cox analysis, or assumed that all the patients with ICDs died within three years after device implantation, the hazard ratios for β_2 -agonist use and relevant covariates were essentially the same as those presented in Table 3.

The combined use of β_2 -agonists and anti-inflammatory steroids has been shown to have complementary effects with a greater benefit at decreasing exacerbations and reducing hospitalizations for patients with bronchial asthma.¹⁷ The combined therapy may allow for improved bronchodilation and anti-inflammatory effects in-comparison to each treatment alone.¹⁸ While our study did not address the respiratory impact from combined therapies, it did identify an increased risk of cardiac events with the joint use of these medications. Anti-inflammatory steroids can increase the transcription of glucocorticoid-regulated genes,^{19,20} which includes β -adrenergic receptors. This up-regulation of β -adrenergic receptors along

with increased receptor stimulation due to β_2 -agonists, may contribute to this augmented risk for cardiac events.

There are several limitations in this observational, retrospective study of patients enrolled in the LQTS Registry. Asthmatic therapy was not randomly assigned, dosage information of the β_2 -agonist therapy was not recorded, and objective measures of the severity of the airway disease were not available. Guidelines have used factors such as symptom control and need for medication in order to categorize the severity of asthma.²¹ We were unable to evaluate the influence of factors such as obesity, smoking, diet and exercise on the adverse outcome of cardiac events. The composite cardiac end point was dominated by syncope, and we could not draw any significant conclusions on the relationship between β -agonists and its propensity to cause mortality due to limited power. We were also unable to evaluate the contribution of specific LQTS genotypes to the risk of cardiac events due to a limited number of genotyped patients receiving β_2 -agonists who experienced cardiac events. The dose of β -blockers utilized in patients with and without asthma was similar, but we cannot draw any conclusions about the appropriate dose of β -blocker therapy that should be used in LQTS patients being treated for asthma.

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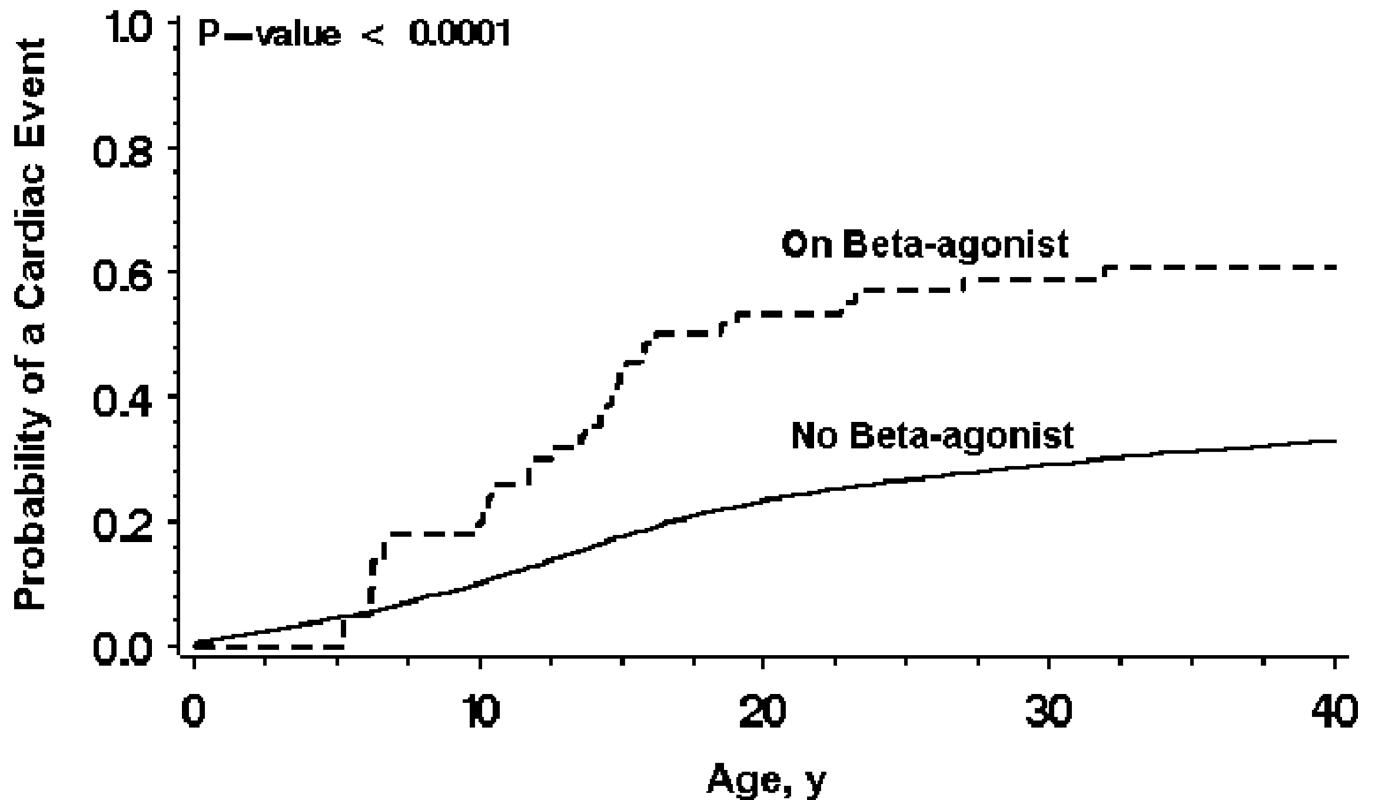


Figure 1.

Mantel-Byar graph of probability of a first cardiac event by use or non-use of beta₂-agonist therapy.

Table 1

Baseline characteristics in long QT syndrome population (QTc 450 msec) by beta-adrenergic therapy

Parameters	Beta-adrenergic Therapy		P-value
	No (N=3186)	Yes (N=101)	
Female	1986 (62%)	74 (73%)	0.03
Age at 1 st ECG recording (years)	28 ± 22	19 ± 13	< 0.001
ECG data			
QTc baseline (msec)	494 ± 47	507 ± 60	0.04
RR baseline (msec)	829 ± 209	786 ± 215	0.02
Asthma	198 (6%)	93 (92%)	< 0.001
Congenital Deafness	57 (2%)	3 (3%)	0.43
LQTS mutations *	(n=1005)	(n=31)	0.61
LQT1	522 (52%)	19 (61%)	
LQT2	365(36%)	8 (26%)	
LQT3	90 (9%)	3 (10%)	
Other	17 (2%)	0	
Multiple Mutations	11 (1%)	1 (3%)	
Medical Interventions			
β-blockers	1555 (49%)	67 (66)	< 0.001
Implanted defibrillator	300 (9%)	18 (18%)	0.005
Pacemaker	207 (6%)	15 (15%)	< 0.001
Left cardiac sympathectomy	107 (3%)	2 (2%)	0.77
1 st Cardiac Event	1360 (43%)	60 (59%)	< 0.001
Syncope	1242 (39%)	59 (58%)	< 0.001
Aborted cardiac arrest	88 (3%)	1 (1%)	0.53
LQTS-related death	30 (1%)	0	0.33
Age at 1 st cardiac event, years	14 ± 10	13 ± 8	0.26

Values are mean ± SD where indicated.

* Mutation identification was available in 1036 patients, and the percentages in the specific genotypes are relative to the number of genotyped patients in each therapy group. The p-value refers to the difference in the distribution of the mutational genotypes by Chi square analysis.

Table 2Prescribed β -blocker dose in long QT syndrome patients by beta-adrenergic therapy

Beta-blockers	Beta ₂ -adrenergic Therapy	
	No	Yes
Atenolol	50 ± 35 mg (n=594)	57 ± 51 mg (n=23)
Metoprolol	85 ± 81 mg (n=210)	83 ± 65 mg (n=7)
Nadolol	61 ± 52 mg (n=468)	62 ± 44 mg (n=10)
Propranolol	82 ± 80 mg (n=742)	96 ± 47 mg (n=8)

Values are mean ± SD.

Table 3

Multivariate Cox model for cardiac events in long QT syndrome patients

Factor	Hazard Ratio	95% CI	P-value
Time-dependent β_2 -agonist therapy (yes:no)	2.00	1.26 – 3.15	0.003
Males:Females (< 13 years of age)	1.47	1.28 – 1.69	< 0.0001
Females:Males (> 14 years of age)	2.43	1.97 – 2.99	< 0.0001
QTc > 500msec:QTc \leq 500msec	1.92	1.73 – 2.13	< 0.0001
Asthma: No asthma	1.16	0.97 – 1.40	0.11
Time-dependent β -blocker use (yes:no)	1.03	0.82–1.29	0.81

* Asthma was forced into the model even though it had an insignificant p-value to show the independent contribution of β_2 -agonist therapy.