Journal of Cystic Fibrosis 15 (2016) 192 – 195

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Short Communication

An evaluation strategy for potential QTc prolongation with chronic azithromycin therapy in cystic fibrosis☆

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Received 12 July 2015; revised 24 October 2015; accepted 23 November 2015
Available online 12 December 2015

Abstract

Chronic azithromycin therapy is recommended for CF patients with persistent *Pseudomonas aeruginosa* colonization. Other macrolide antibiotics have been reported to cause QT prolongation, but cardiac effects of azithromycin have not been studied in pediatric populations. We analyzed changes in QTc interval after starting chronic azithromycin in a pediatric CF population. Adolescent males showed increased QTc intervals after initiation of therapy. Given the possible effects of azithromycin on the QTc interval, particularly in patients predisposed to cardiac events, we suggest that the QTc interval of CF patients should be monitored throughout the course of chronic azithromycin.
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Keywords: Azithromycin; QTc prolongation; QTc interval; Macrolide; Cystic fibrosis

1. Introduction

Chronic azithromycin therapy improves lung function and decreases pulmonary exacerbations in CF patients colonized with *Pseudomonas aeruginosa* [1]. However, macrolide antibiotics may cause prolongation of the QTc interval [2] and may increase risk for polymorphic ventricular tachycardia (Torsades de Pointes) and subsequent death [3–5].

Multiple cardiac events, including Torsades de Pointes, related to QTc prolongation have been associated with prescription of azithromycin [6]. A 2012 study found that those taking azithromycin were at elevated risk for cardiovascular death and death from any cause during the five days of therapy [7,8]. Other studies have found similar associations, but these relationships have not been assessed in pediatric populations (Supp. Table 1).

Thus, although the benefits of chronic azithromycin therapy in pediatric CF patients are established, the risks of related cardiac events in this population are unknown. We propose the use of a simple algorithm to assess the safety of beginning and continuing chronic azithromycin therapy in patients with CF.

2. Methods

2.1. Study

The participants of the study are patients, 0–21 years of age, on chronic azithromycin therapy at the Central Connecticut Cystic Fibrosis Center.

2.2. Goal of study

The goal of the study is to determine whether chronic administration of azithromycin to pediatric CF patients led to predictable increases in QTc intervals with clinical significance.

☆ *Abstract presented at 2013 North American Cystic Fibrosis Conference (Salt Lake City, Utah)*: "QT Prolongation in Chronic Azithromycin Therapy: A Rational Monitoring Strategy." Lenehan, P.; Lapin, C.D.; Drapeau, G.; Leopold, H.; Bhandari, A.; Schramm, C.; Collins, M. Pediatric Pulmonogy; Supplement 36, 2013. (Abstract)

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http://dx.doi.org/10.1016/j.jcf.2015.11.012
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2.3. Study design

EKG monitoring began in 2009. The study began as a retrospective chart review in 2011 and became a prospective study thereafter. Pre- (if patients were not already on chronic azithromycin) and post-EKGs were obtained and used to calculate the ΔQTc (ΔQTc = post-azithromycin QTc − pre-azithromycin QTc).

2.4. Protocol

IRB approval and informed consent were obtained. EKGs were performed at routine visits and interpreted by a pediatric cardiologist. QTc interval was calculated using Bazett's formula: QTc = QT interval / √(RR interval). QTc ranges were defined as follows: normal—QTc ≤ 440 ms; borderline—QTc 441–460 ms; prolonged—QTc > 460 ms [3,9–11]. Normal variation in QTc for gender is not necessarily applicable in pediatric patients [10,11].

Patients were divided for analysis by age (childhood 0–12 years, adolescence 13–21), gender, and CF genotype (homozygous for the ΔF508 mutation [ΔF/ΔF], heterozygous for the ΔF508 mutation [ΔF/O], and no copies of the ΔF508 allele [O/O]).

2.5. Statistical analysis

Data were analyzed using StatView statistical software (version 5.0.1; SAS Institute, Cary, NC). QTc intervals were compared pre- and post-azithromycin by paired t-tests. Regression analyses and Bland–Altman plots [12] compared QTc intervals pre and post azithromycin. Since most subgroup data failed the Shapiro Wilk test for normality, baseline QTc intervals and changes in the interval were compared between subgroups of patients by the Mann–Whitney U test for 2 groups or the Kruskal–Wallis test for more than 2 groups. In all analyses, p values of <0.05 were considered statistically significant. The data were reported as mean ± standard deviation or as median with 25%–75% interquartile range (IQR) depending on the type and distribution of the variables.

Our power analysis assumed the difference between a normal QTc interval (<440 ms) and a clinically prolonged QTc interval (>460 ms) represented greater than 2 standard deviations of the population's QTc intervals. Accordingly, the standard deviation for a QTc measurement would be ±10 ms. Thus, with paired t-testing, 34 patients were required to demonstrate a 5 ms increase in their QTc intervals, or 10 patients to demonstrate a 10 ms increase at a confidence value of 95% and power of 80%.

3. Results

The study included 56 pediatric patients, 25 females and 31 males. There were 33 children and 23 adolescents. There were 24 ΔF/ΔF patients, 21 ΔF/O, and 11 O/O. No differences were found between the retrospective (n = 24) and prospective patients (n = 33); however, all O/O genotype patients were in the prospective study (Supp. Table 2).

No patients had clinically prolonged QTc intervals with azithromycin therapy, but 4 patients had borderline post-azithromycin elevated intervals (i.e., QTc > 440 ms). These 4 patients did not differ from those with normal QTc intervals in any baseline parameter, and their pre-azithromycin QTc intervals were not statistically significantly higher. Interestingly, all 4 patients had at least one ΔF508 mutation. Eighteen patients were receiving additional potential QTc-prolonging drugs (principally long-acting beta agonists [n = 11]), but use was similar between patients with normal versus borderline post-azithromycin QTc intervals (Table 1).

For the entire study population, ΔQTc was 1 ± 18 ms (p = 0.78 by paired t-test). Regression analyses indicated that pre-QTc values were directly related to post-QTc values (p = 0.008; Fig. 1A). However, Bland Altman analysis indicated the absence of any fixed or proportional influence of azithromycin on the QTc interval (Fig. 1B).

We found no statistically significant difference in pre-QTc or ΔQTc values related to CF genotype (Supp. Fig. 2A). Females had a significantly higher pre-QTc (median 432; IQR 410–438) than males (median 410; IQR 394–420; p = 0.018). Neither males nor females showed a significant ΔQTc after azithromycin therapy, but there was a trend toward difference between genders (p = 0.08), with males more likely to experience an increase in QTc interval than females (Supp. Fig. 2B). We found no effect of age on pre-QTc, post-QTc, or ΔQTc (Fig. 2A). However, adolescent males had significantly increased QTc intervals after starting chronic azithromycin (p = 0.047), with a median change (IQR) of +12 (+4 to +26) ms (Fig. 2B).

4. Discussion

Using this standardized approach, we found that chronic azithromycin therapy did not prolong the QTc interval of pediatric CF patients. Only adolescent males demonstrated an increase in QTc interval on chronic azithromycin.

We conducted this study because previous studies have associated azithromycin with increased risk for arrhythmias and

Table 1
Characteristics of patients with normal and borderline elevated QTc intervals post-azithromycin. Data represent median values and interquartile ranges; p values derived by Mann–Whitney U or chi-square testing. The row labeled "AZI 250: 500" provides the number of patients in each group taking 250 mg and 500 mg of azithromycin three times weekly, respectively. "Other QTc drug" demonstrates concomitant use of other potential QTc-prolonging drugs.

	Normal QTc (47)	Borderline long QTc (4)	p
Age (years)	11.0 (6.5–13.9)	12.1 (9.4–13.1)	0.89
M: F	26: 21	2: 2	>0.99
ΔF/ΔF: ΔF/O: O/O	22: 16: 9	2: 2: 0	0.59
QTc pre-AZI (ms)	413 (396–428)	435 (418–443)	0.25
QTc post-AZI (ms)	412 (404–425)	446 (443–448)	0.0010
QTc post–pre (ms)	−6 (−14 to +12)	+10 (+6 to +17)	0.52
AZI 250: 500	28: 19	2: 1	>0.99
Other QTc drug (Y:N)	17: 30	1: 3	>0.99

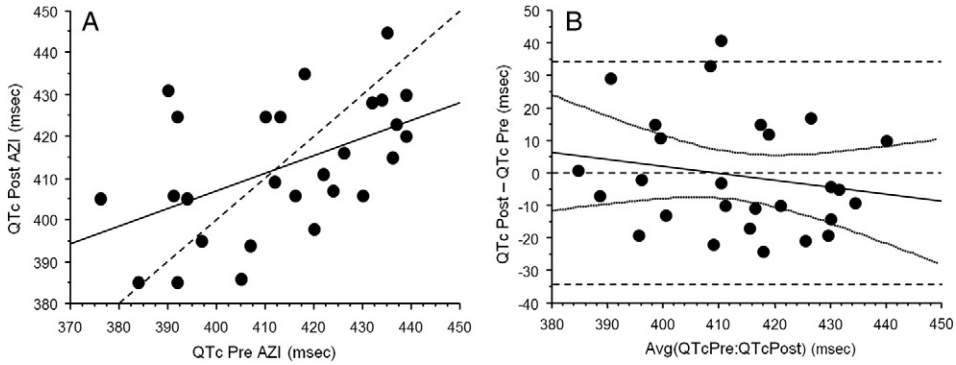

Fig. 1. Correlation between QTc intervals obtained before (QTc pre) and after (QTc post) starting chronic azithromycin (AZI) therapy. (A) QTc post values were directly related to QTc pre values ($R^2 = 0.25$), with mean ± S.E.M. slope 0.43 ± 0.15 ($p = 0.0075$) and intercept 236 ± 61 ms ($p = 0.0007$) compared to the line of identity (dashed line). (B) Bland Altman plot of the difference between paired post and pre QTc values versus the average of the paired pre and post values. Note the absence of any fixed (i.e., vertical displacement) or proportional (i.e., slope) difference of azithromycin on the QTc interval.

other cardiac events in adults within 5 days of the start of therapy [13], and clarithromycin has been shown to significantly increase the QTc interval of pediatric patients 24 h after treatment initiation [14]. Notably, patients who have developed arrhythmias in association with azithromycin have typically been on concomitant QT-prolonging drugs [15–17] or have had cardiac conditions predisposing them to arrhythmias [18–20].

Because we obtained post-EKGs during routine visits (2–6 months after the initiation of chronic azithromycin), it is possible that a transient azithromycin-induced QTc prolongation was not detected [13]. Further, our study population did not include enough patients on concomitant non-LABA QTc prolonging medications to draw conclusions about a possible additive effect. As such, our results should not be interpreted as decisive evidence against an increased risk for adverse cardiac events with chronic azithromycin.

Our simple algorithm was developed (Supp. Fig. 3) to facilitate the safe initiation and continuation of chronic azithromycin while adding little to a CF patient's burden of care. Patients are screened for a congenitally prolonged QTc interval prior to initiation of azithromycin and monitored as therapy is continued or adjusted. Currently, we use the same normal ranges for male and female patients as there is debate over whether gender influences the QTc interval in children [20]. In our study females did in fact have higher mean and median QTc intervals, as some other studies have suggested; however, this is not evidence that the range of normal (i.e. safe) QTc intervals is higher for females than males. Based on our limited population, it seems that using only a screening EKG prior to chronic azithromycin therapy may be sufficient. If azithromycin is found to have only a transient effect on QTc interval or to enhance the QTc-prolonging effects of other drugs, then the algorithm would be modified and patients taking such medications concurrently would be monitored more closely.

Acknowledgments

We recognize with sincere gratitude our patients, families and the outstanding staff at the Central Connecticut Cystic Fibrosis Center.

We appreciate the help of the CCMC Department of Cardiology in interpreting our EKGs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2015.11.012.

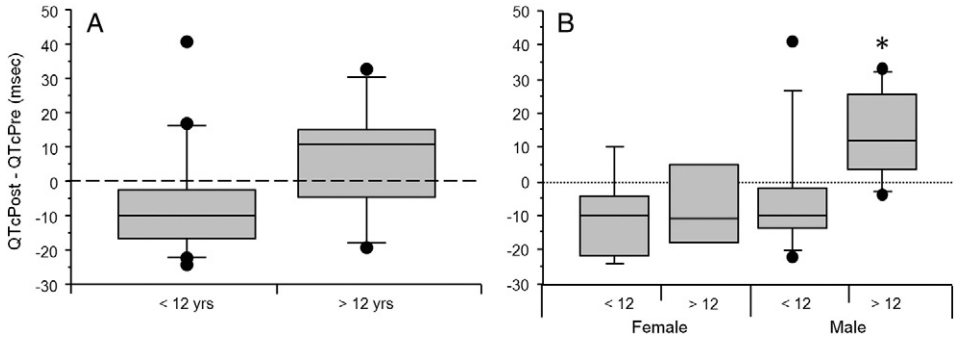

Fig. 2. Influence of age on change in QTc with azithromycin therapy. (A) The ΔQTc was greater in patients >12 years of age (n = 11) compared to patients <12 years of age (n = 16). $p = 0.046$ by Mann–Whitney U test. (B) ΔQTc increased significantly in adolescent male patients (n = 7; *$p = 0.047$ vs. 0 by Wilcoxon Signed Rank testing), as compared to child male (n = 11), adolescent female (n = 4), and child female patients (n = 5). Box plots depict median values (central lines), interquartile ranges (shaded boxes), 10th and 90th percentiles (bars), and outlying points. $p = 0.043$ by Kruskal–Wallis test.

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