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Research paper

Short-term azithromycin use is associated with QTc interval prolongation in children with cystic fibrosis

Asım Enhoş[a,*], Hazar Doğuş Kus[b], Can Yilmaz Yozgat[c], Erkan Cakır[d], Hakan Yazan[e], Ahmet Berk Erol[f], Ufuk Erenberk[b], Yilmaz Yozgat[g]

[a] Department of Cardiology, Istanbul Medipol University, Istanbul, Turkey
[b] Department of Pediatrics, Bezmialem Vakif University, Istanbul, Turkey
[c] Faculty of Medicine, Maltepe University, Istanbul, Turkey
[d] Department of Pediatric Pulmonology, Istinye University Hospital, Liv Vadi Hospital, Istanbul, Turkey
[e] Department of Pediatric Pulmonology, Istanbul Medipol University, Istanbul, Turkey
[f] Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey
[g] Department of Pediatric Cardiology, Istanbul Medipol University, Istanbul, Turkey

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ABSTRACT

Background: Azithromycin is used for children with cystic fibrosis (CF) for its immunomodulatory and anti-inflammatory action. This study investigated the short-term alterations in QTc interval associated with azithromycin prophylaxis in pediatric patients with CF.
Methods: This study included 121 patients with mild CF, of whom 76 received azithromycin (patient group) and 45 did not receive azithromycin (control group). The patient and control groups were categorized according to age as under 12 years of age and over 12 years of age. The first presentation measured all the patient and control groups at basic QTc time intervals. The QTc intervals of all patients were then remeasured systemically at 1, 3, and 6 months. Age categories and QTc intervals that were calculated at each month in the patient and control groups were compared statistically.
Results: A statistically significant difference was detected in the patient group between the initial QTc interval time and the electrocardiogram (ECG) findings in the first and third months after prophylaxis treatment ($p < 0.001$; $p = 0.01$). However, no statistically significant difference was detected in the sixth month ($p > 0.05$) in all groups. Almost all of the children's QTc intervals were within normal range and within the safety zone (under 0.44 s). No statistically significant difference was detected in the control group between the initial ECG and the QTc intervals measured at 1, 3, and 6 months.
Conclusion: Short-term use of azithromycin prophylaxis in pediatric patients with mild CF slightly increased the QTc interval in the first and third months of follow-up. Nevertheless, all QTc interval changes fell within the safety zone. Notably, 1 month of follow-up treatment should be performed to check for any alteration in the QTc interval. If increased QTc interval duration is not detected in the first month, azithromycin prophylaxis can be safely prescribed.

Introduction

Azithromycin is a broad-spectrum antibiotic with a long half-life. It is generally used to reduce respiratory, enteric, and genitourinary infections. Azithromycin has additional beneficial immunomodulatory and anti-inflammatory effects [1] As such, it is prescribed to pediatric patients with respiratory inflammatory disorders such as cystic fibrosis (CF).

Azithromycin treatment should be prescribed for at least 6 months in patients with clinical symptoms of CF to improve respiratory function and massive debilitation in respiratory exacerbations [2]. Today, for patients older than 6 years, regardless of CF severity, if traces of peribranchial cuffing or abnormalities are present on the chest X-ray, azithromycin prophylaxis should be immediately initiated because of its antipseudomonal and anti-inflammatory properties [3].

Acquired long QTc syndrome is characterized by an alteration of ventricular arrhythmia (torsade de pointes and ventricular fibrillation) due to medication, which prolongs the QTc interval in a patient's electrocardiogram (ECG). The diagnosis is based on the QTc interval being greater than 0.44 s. When medication affects the QTc

* Corresponding author at: Istanbul Medipol University, Faculty of Medicine, Medipol Mega University Hospital, Department of Cardiology, TEM Avrupa Otoyolu Goztepe Cikisi, No: 1, 34214 Bagcilar, Istanbul, Turkey.
E-mail address: asimenhos@hotmail.com (A. Enhoş).

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Table 1
Pulmonary function tests and clinical scores of patients and controls.

	Patients		Controls		*p*
	Mean	Minimum–Maximum	Mean	Minimum–Maximum	
FEV_1	1.32	(0.80–3.5)	1.34	(0.78–3.7)	0.386
FEV_1%	85.00	(70–120)	85.00	(70–120)	0.756
FVC	1.40	(0.8–4.2)	1.38	(0.7–4.1)	0.115
FVC%	83.45	(72–120)	83.42	(72–118)	0.547
SK score	85.36	(70–95)	85.28	(68–93)	0.483

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; SK score: Shwachman–Kulczycki score.

interval, the measured QTc should be less than 0.44 s in an ECG strip. If it is under 0.44 s, it is considered to be within the safety zone [4].

Macrolide antibiotics prolong the cardiac QTc interval, leading to acquired long QTc syndrome. Initial concerns regarding the relationship between azithromycin and cardiovascular risk arose from previous case reports. One of the critical case reports was published by Ray et al., which specifically led to the Food and Drug Administration (FDA) Safety Announcement regarding the association of "azithromycin and the risk of potentially fatal heart rhythms," dated December 3, 2013 [5]. The results prompted the FDA to issue a warning to prescribers. Furthermore, observational studies were conducted with inpatient populations that use azithromycin excessively. The results of these studies were intriguing and showed an increased risk of cardiovascular disorders in patients treated with azithromycin [6–8].

According to the literature, 6–15 months of azithromycin use is considered long-term use [9,10], whereas short-term therapy is described as <6 months of use. Few studies with pediatric populations have investigated the effects of azithromycin use on the QTc interval. Therefore, we decided to study the possible short-term effects of azithromycin prophylaxis on myocardial repolarization in children with mild CF. This study investigated alterations in the QTc interval with short-term use of azithromycin prophylaxis in pediatric patients with mild CF, regardless of the safety zone.

Patients and methods

Study participants

This prospective study was initiated after the approval of the ethics committee and was conducted between October 2018 and September 2020. The pediatric pulmonology department was responsible for the patients in this study. The study comprised 151 patients with mild CF; 29 patients were excluded for not following the study's protocol, for developing side effects (abdominal pain, diarrhea, and vomiting), or for incomplete medication. During ECG follow-ups, clinicians asked whether patients were receiving regular azithromycin treatment. All of the patients were clinically stable; none had a respiratory exacerbation within the previous 3 months. All of the patients with CF had genotype and sweat test confirmation of their diagnosis. According to the European Respiratory Society classification, mild CF was characterized by a forced expiratory volume in 1 s (FEV_1) of ≥70 % (Table 1). A total of 76 patients with mild CF were included in the patient group, and all received azithromycin prophylaxis 3 days a week for 6 continuous months (Monday/Wednesday/Friday). The ECG recordings were obtained at 0, 1, 3, and 6 months of treatment. ECGs were recorded on days when azithromycin treatment was not administered. Among the group with mild CF in this study, 45 patients who did not use azithromycin were included as the control group. Both groups comprised patients whose age, gender, and body mass index (BMI) were similar. The demographic characteristics of all patients are shown in Table 2.

The patient and control groups were categorized according to their ages as under 12 years of age and over 12 years of age. All patients used azithromycin prophylaxis in the patient group—the first presentation measured all the patient and control groups at basic QTc intervals. The QTc intervals of all patients were then remeasured systemically at 1, 3, and 6 months. Age categories and QTc intervals that were calculated at each month in the patient and control groups were compared statistically. The patient group comprised 34 male patients and 42 female patients. The patients' ages were between 8 and 17 years. All patients and/or parents who participated in this study were informed verbally about the purpose of the study and the type of practices to be performed, and their written informed consent was obtained. The azithromycin dosing regimens were administered at the pediatric pulmonary clinic 3 days (Monday/Wednesday/Friday) a week. Patients weighing 10–40 kg were administered 250 mg azithromycin and patients weighing ≥40 kg, 500 mg azithromycin was orally administered.

Table 2
Comparison of demographic characteristics of patients and controls.

Participants, *n*	76 (patient group)	45 (control group)	*p*
Gender	42 (55.5 %)	27 (55%)	0.675
Age (years)	10.53±5.63	10.33±6.73	0.456
Body weight (kg)	27.9 ± 12.10	25.7 ± 13.10	0.087
Height (cm)	132.0 ± 17.59	130.0 ± 19.61	0.515
BMI	16.02±2.52	15.24±2.4	0.08

*Values are expressed as mean± SD; (*): statistically significant.
BMI: body mass index.

Electrocardiography

A standard 12-lead ECG (Cardiofax GEM, Model 9022 K; Nihon Kohden, Tokyo, Japan) was recorded at a speed of 25 mm/s and an amplitude of 1 mV/cm while the patient was in the supine position. The ECG recordings were scanned and transferred to a personal computer. After zooming in ×400 using Adobe Photoshop software, measurements were taken directly from these ECG tracings by two blinded pediatric cardiologists. The QT interval was defined as the measurement from the onset of the QRS complex to the end of the T wave. The end of the T wave was determined to be the intersection point of the isoelectric line and the tangent line at the maximum downward slope of the T wave. Without the T wave, the QT interval was not measured. The corrected QT interval was calculated using Bazett's formula: QTc = QT interval /√ (RR interval) [1,11,12]. QTc was calculated in at least eight leads, including leads I, II, and V_5. The most prolonged QTc interval was recorded as the patient's QTc interval.

Pulmonary function tests

Spirometry was performed on all patients with CF. Patients with CF were clinically classified using the FEV_1 value, modified by the Shwachman–Kulczycki score [12]. Spirometry (Winspiro, Rome, Italy) was performed for patients older than 8 years. Forced vital

Table 3
Comparison of QTc duration in children with mild cystic fibrosis, with or without short-term azithromycin treatment.

Age group		Patient group	*N*	Mean	SD	*p*
Under 12 years old	Day Zero	patient	41	0.39190	0.021731	0.81
		control	29	0.38472	0.014950	
	1st month	patient	41	0.41432	0.018399	**<0.001**
		control	29	0.38707	0.012484	
	3rd month	patient	41	0.39890	0.018747	**0.001**
		control	29	0.38370	0.013743	
	6th month	patient	41	0.39520	0.021981	0.69
		control	29	0.38741	0.011587	
Over 12 years old	Day Zero	patient	35	0.38885	0.021105	0.59
		control	16	0.38325	0.017212	
	1st month	patient	35	0.41194	0.019130	**<0.001**
		control	16	0.38269	0.015041	
	3rd month	patient	35	0.39217	0.018051	**<0.001**
		control	16	0.37559	0.012925	
	6th month	patient	35	0.38377	0.021716	0.205
		control	16	0.37581	0.017475	

SD: standard deviation.
*Values are expressed as mean± SD.
*Values are expressed in seconds.

capacity and FEV_1 were measured. The best test measurement was usually recorded after the third time using the spirometer value. Pulmonary disease was classified as mild in cases of a FEV_1 of ≥70 according to the European Respiratory Society classification [13].

Statistical analysis

SPSS 18.0 was used (SPSS Inc., Chicago, IL, USA) for statistical analysis. The data distribution pattern was evaluated using the Kolmogorov–Smirnov test. Where appropriate, values are expressed as mean ± SD or median (interquartile range). ANOVA was the appropriate test for repeated QTc measurement. QTc intervals were compared before and after azithromycin administration by paired *t* tests and the Wilcoxon signed-rank test. A value of $p < 0.05$ was considered statistically significant.

Results

In the patient group, the median age was 11 years (min 8; max 17), and 42 were female (55.5 %). Both the patient and control groups comprised patients whose age, gender, and BMI were similar. Pulmonary function tests and clinical score findings for the patient and control groups are presented in Table 1. Table 2 presents a comparison of the demographic characteristics between the patient and control groups.

A statistically significant difference was not detected between the initial QTc interval in the patient and control groups under the age of 12 years and the patient and control group over the age of 12 years. There was a statistically significant difference between the patient group and control group in terms of QTc interval values measured in patients under 12 years of age in the first month (QTc 0.414 ± 0.018 s and 0.387 ± 0.012 s, $p < 0.001$). Similarly, there was a statistically significant difference between the patient group and control group in terms of the QTc interval measured in patients over 12 years of age in the first month (QTc 0.411 ± 0.019 s and 0.382 ± 0.015 s, $p < 0.001$). In addition, there was a statistically significant difference between the patient group and control group regarding the QTc interval measurements in the third month in patients under 12 and over 12 years of age (QTc 0.398 ± 0.02 s and 0.383 ± 0.013 s, $p = 0.01$; QTc 0.392 ± 0.018 s and 0.375 ± 0.012 s, $p < 0.001$).

However, no statistically significant difference was detected in the 6-month QTc measurements between the patient group and control group in patients under 12 and over 12 years of age (QTc 0.395 ± 0.021 s and 0.387 ± 0.017 s, $p = 0.69$; QTc 0.383 ± 0.021 s and 0.375 ± 0.017 s, $p = 0.2$).

We found that all pediatric patients with mild CF had slightly prolonged QTc intervals in the first and third months of follow-up. However, all QTc interval changes fell within a reasonable value under 0.44 s. All statistical results are listed in Table 3. None of the patients had any arrhythmias, and none of the patients' QTc values exceeded 0.44 s. The patients had no electrolyte disturbance of potassium (3.65 ± 0.61 mmol/L) or magnesium (0.74 ± 0.18 mmol/L). All patients tolerated the medication exceptionally well. Table 3 compares the QTc duration in children with mild CF, both with and without short-term azithromycin treatment, and in different age groups.

Discussion

Previous studies of pediatric and adult patients have shown that macrolide antibiotics prolong the cardiac QTc interval [10,14-16]. This association may increase the risk of polymorphic ventricular tachycardia (torsade de pointes) and the possibility of subsequent death [4,5,7,8]. In addition, a 2012 study reported that azithromycin elevates the risk of cardiovascular death and may cause death during the first 5 days of therapy [5,17]. Adult patients with CF are exposed to various concurrent medications with azithromycin, many of which can prolong QTc. [18]. There have been numerous studies showing that azithromycin can prolong QTc in young adults. Similar to these studies, our pediatric patients with mild CF had slightly prolonged QTc intervals in the first and third months of follow-up. However, all QTc interval changes fell within a reasonable value in the safety zone.

In our study, pediatric patients with mild CF were not administered any additional medications, and there was no electrolyte disturbance. Thus, we concluded that the increase in QTc interval duration was caused by the effects of the medication on heart repolarization. However, no statistical difference was detected in the control group between the initial ECG and the measurements at 1, 3, and 6 months.

Few studies have investigated the effects of azithromycin on ventricular repolarization in animals. Ohara et al. conducted a study evaluating the effect of high-dose azithromycin on QTc prolongation and cardiovascular endpoints in a translational canine model [19]. High-dose azithromycin transiently prolonged QTc by approximately +20 ms and delayed ventricular repolarization, but azithromycin administration did not induce torsade de pointes [19].

Lenehan et al. [10] conducted the first pilot study in 2016 to analyze the relationship between QTc prolongation and the effects of azithromycin prophylaxis on pediatric patients. This study aimed to determine whether systemic administration of azithromycin to 56 pediatric patients with CF might lead to anticipated increments in QTc intervals with clinical significance. They divided their patients into two groups and grouped the patients according to whether they were under or over 12 years old. They recorded the patients' initial ECG before the administration of azithromycin. Later, once the administration of azithromycin had begun, the patients were asked to return to the clinic at 2 and 6 months to check for any existing QTc prolongation. The authors found that long-term azithromycin therapy did not prolong the QTc interval in pediatric patients with CF under 12 years of age. Only adolescent boys demonstrated significant increases in their QTc intervals on long-term azithromycin.

In contrast to these results, our prospective study detected a slight prolongation of the QTc duration between the patients' ECGs before and after azithromycin administration. Also, the design of our study was completely different from that of Lenehan et al.

First, our study was conducted prospectively: Before the initiation of any medications, the ECG of patients was recorded, and the patients treated with azithromycin were monitored closely. In addition, we obtained the QTc measurements at 1, 3, and 6 months. In our study group, none of the patients used any other medications, and the severity of the patients' condition was only mild CF. As a result, we concluded that slight prolongation of the QTc interval in our patients was related to azithromycin prophylaxis. In the first month of follow-up, the patients' QTc results were significantly prolonged compared with the initial QTc results. We did not detect any statistically significant differences at the 6-month follow-up.

The underlying mechanisms of azithromycin prophylaxis prolonging the QTc interval in patients with CF have yet to be elucidated. Various potential mechanisms have been suggested as explanations for the prolongation of the QTc interval. It is widely recognized that a strong correlation exists between drug-induced QTc interval prolongation and pharmacological inhibition of the cardiac potassium channel [12,20]. The impairment of action potential duration in cardiac cells causes a subsequent increase in the transmural dispersion of repolarization by inhibiting potassium channels [21]. Our study concluded that the main reason for prolongation of the QTc interval in our patients was the pharmacological inhibition of the cardiac potassium channel due to the use of azithromycin and, thereafter, the notable increase in the transmural dispersion of repolarization. Krasemann et al. [22] conducted a study on various QTc intervals in healthy children. The corrected QT interval was calculated from 24-h ECGs obtained from 282 healthy children aged 6 months to 18 years. The authors concluded that the QTc interval alterations changed little over 24 h and remained remarkably constant despite significant heart rate changes in healthy children. In addition, the study did not show significant differences between sexes in any age group. In our study, the patients in the control group did not have QTc interval alterations or physiological variances.

In addition, our study investigated azithromycin prophylaxis, which is commonly used in 1-, 3-, and 6-month-old pediatric patients diagnosed with CF, regardless of whether there is an increase in their QTc interval duration. A statistically significant difference in QTc interval measurements was detected between the initial ECG before prophylaxis and the first and third month after the start of prophylaxis treatment.

However, a statistically significant difference was not found in pediatric patients who used azithromycin prophylaxis for more than 3 months compared with those who used it before the initiation of prophylactic treatment. We recommend safe use of azithromycin prophylaxis for pediatric patients with mild CF. A follow-up should be performed after 1 month of treatment to check whether alterations in the QTc intervals are present. If a prolonged QTc interval is not detected in the first month, azithromycin prophylaxis can be safely used as a long-term treatment.

Study limitations

The primary limitation of this study was that it only focused on the QTc prolongation after azithromycin use in pediatric patients with CF. CF is a multisystemic disease, and although we did not perform any additional statistical or clinical study on the course of FEV_1, there is a need for assessment of antibiotic intake, number of pulmonary exacerbations, weight gain, inflammatory markers, and electrolytes. Future studies should focus on more clinical details concomitant with QTc prolongation due to the use of azithromycin.

Conclusions

The short-term use of azithromycin prophylaxis in pediatric patients with mild CF slightly increased the QTc interval in the first and third months of follow-up. Nevertheless, all QTc interval changes fell within a reasonable value in the safety zone. None of the patients had any arrhythmias, and none of the patients' QTc values exceeded 0.44 s. All patients tolerated the medication exceptionally well. Based on our results, 1 month of follow-up should be performed to check whether alterations in the QTc intervals are present. If a prolonged QTc interval is not detected in the first month, azithromycin prophylaxis can be safely administered, with the exception that no other medication with a QTc increase is used. However, if an increase in the QTc interval is detected in the first month after receiving azithromycin prophylaxis, compared with the initial ECG, the prolonged QTc interval should be monitored closely.

Declaration of competing interest

The authors declare there is no conflict of interests.

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