

EFFECT OF AZITHROMYCIN ON QTc INTERVAL IN CHILDREN: AN OBSERVATIONAL PROSPECTIVE STUDY IN LAHORE, PAKISTAN

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ABSTRACT

To determine the effect of the azithromycin on QTc interval in terms of absence or presence of prolongation in children admitted in Children's Hospital Lahore, Pakistan, The study utilized observational prospective study to test the effect of Azithromycin on QTc interval in children, The study was conducted at the general medical unit of the Children's Hospital Lahore within six months after approval from hospital ethical committee, 102 patients visiting the Children hospital Lahore, fulfilling the inclusion criteria, were selected using non-probability consecutive sampling technique. A written informed consent was taken from parents (father or mother) followed by child assent. Detailed history was taken including age, gender, weight, diagnosis, and any underlying chronic ailment. A baseline ECG and serum electrolytes were taken before starting azithromycin. Then, a serial ECG was taken on each day for a total of five days and QTc interval was calculated. All the collected data were entered and analyzed using SPSS (v. 24), The mean age of patients was 6.88 ± 3.44 years with male to female ratio of 1:1.22. The mean value of QTc interval at baseline was 403.90 ± 12.18 ms, after two days it was 402.47 ± 11.87 ms, after three days it was 402.94 ± 12.02 ms, after four days it was 403.80 ± 12.12 ms, and after five days it was 405.90 ± 18.77 ms. In current study, the QTc prolongation was observed in six (5.9%) patients, It was concluded that there was no statistically significant effect of azithromycin on the ventricular repolarization parameters (QTc) on electrocardiogram (ECG) in pediatric patients treated with azithromycin.

Keywords: Azithromycin, QTc prolongation, children, Lahore, Pakistan

INTRODUCTION

Azithromycin, discovery from class of the macrolides, is one of the most important new drug of the 20th century.⁽¹⁾ It works by inhibiting bacterial protein synthesis, delayed inhibitory effects, immunomodulation, and anti-fibrotic effects.^(2, 3) Azithromycin is commonly prescribed in treatment of lower and upper respiratory tract, skin, and soft tissue infections. It is also being used to manage uncomplicated urethritis/cervicitis associated with Neisseria gonorrhoea, Chlamydia trachomatis or Ureaplasma urealyticum, Lyme disease, and viral infections as well.⁽³⁾

It was widely used during Covid-19 pandemic for SARS-CoV-2 infection, though evidence on its efficacy is still lacking.⁽³⁾ Azithromycin is

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administered once a day as it is released slowly in blood⁽⁴⁾ It is among the antibiotics most frequently prescribed to children.⁽⁴⁾ An analysis in 2020 revealed that roughly 66.8 million antibiotics were given to children aged less than 19 years in the USA. Among them, Amoxicillin and Azithromycin were the most commonly prescribed drugs.⁽⁵⁾

Azithromycin is generally well accepted antibiotic, although many of its typical minor adverse effects include dizziness, headache, vomiting, diarrhea and nausea.⁽⁶⁾ Prominent side effects of azithromycin encompass torsades de pointes, hypersensitivity responses, and ototoxicity.⁽⁶⁾ Multiple studies in the literature have also

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documented instances of liver damage caused by azithromycin.⁽⁷⁾ Research in the adult population also showed that it has a QTc prolonging effect.⁽⁸⁾ Patients with QTc interval prolongation may experience lightheadedness, dizziness, palpitation, or syncope.⁽⁶⁾ In a study conducted by Ramireddy et al., out of 490 adult patients, 12% experienced QTc prolongation of which incidence was increased in patients taking hydroxychloroquine and azithromycin in combination than taking either of the drugs alone.⁽⁹⁾

In another study azithromycin use in adults was seen to cause sudden cardiac death by prolongation of QT interval and triggering ventricular arrhythmias and torsades de pointes.⁽¹⁰⁾ It can prolong ventricular repolarization by altering the myocyte action potential and predisposing to malignant ventricular arrhythmias.⁽¹⁰⁾ Despite these rare adverse effects, azithromycin remains classified by the World Health Organization (WHO) as one of the most safe and efficacious drugs in the present healthcare system.⁽⁹⁾

To our best knowledge till date, a single study has been done on children that documented azithromycin's effect on QTc interval. The study included 56 pediatric patients, 25 females and 31 males of cystic fibrosis who were taking azithromycin prophylactically. No patient had clinically significant prolonged QTc intervals with azithromycin therapy, but four patients had borderline post-azithromycin elevated intervals (i.e., QTc 441-460 ms).⁽¹¹⁾

The present study was strictly limited to the pediatric population to check the effect of azithromycin on QTc interval because of excessive use of azithromycin in children. The study will be beneficial in determining whether azithromycin used under ECG monitoring could avoid adverse outcomes or not.⁽¹²⁾

METHODOLOGY:

After approval from ethical committee of the Hospital, the present observational prospective study was conducted. 102 patients visiting the

Children Hospital Lahore were selected using non-probability consecutive sampling technique. Only those children were selected who fulfilled the inclusion criteria i.e., children of age between 2-12 years having any gender and diagnosed with upper or lower respiratory tract infections, skin and soft tissue infections, and urinary tract infection.

The study excluded children with known QTc interval prolongation syndrome, diagnosed with enteric fever, taking any other drug known to prolong QTc interval e.g. ciprofloxacin, artemether, fluconazole, ondansetron & sildenafil etc., allergic to azithromycin, critically ill patients i.e. on cardiopulmonary supports and having sepsis.

A written informed consent was taken from parents (father or mother) followed by child assent and detailed history were taken including age, gender, weight, diagnosis, and any underlying chronic ailment. A baseline ECG and serum electrolytes were taken before starting azithromycin. Then, a serial ECG was taken on each day for a total of five days and QTc interval was calculated using the following formula:

$$QTc = QT / \sqrt{RR}$$

Cardiac monitoring and consultation were taken for these patients, serum electrolyte was obtained, and correction was done if required. All the collected data was entered and analyzed using SPSS (v. 24). Numerical variables i.e., age, weight, and QTc interval were presented as Mean \pm SD. Categorical variables i.e., gender and presence of prolongation was presented as frequency and percentages. To check significant differences, t-test and chi-square test were used with a 5% margin of error ($p < .05$).

RESULTS:

The mean age of 102 patients was 6.88 ± 3.44 years and mean weight was 20.65 ± 10.32 kg. Out of 102 patients, 46 (45.1%) were male and 56 (54.9%) were female with male to female ratio as 1:1.22. In current study, most of the patients were from 2-5 years age group i.e. 44.1%.

Table-1: Results of descriptive statistics

Variables		Frequency	Percent
Age Groups	2-5 years	45	44.1
	6-10 years	34	33.3
	11-12 years	23	22.5

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Age (years), Mean \pm SD		6.88 \pm 3.44	
Weight (kg), Mean \pm SD		20.65 \pm 10.32	
Gender	Male	46	45.1
	Female	56	54.9
	Total	102	100.0

It was found that the mean value of QTc interval at baseline was 403.90 \pm 12.18 ms, after two days it was 402.47 \pm 11.87 ms, after three days it was 402.94 \pm 12.02 ms, after four days it was 403.80 \pm 12.12 ms and after five days it was 405.90 \pm 18.77

ms. In current study, QTc prolongation was observed in 6 (5.9%) patients. There was also no statistically significant association of age and gender with QTc prolongation.

Table-2: Results of QTc interval (ms)

Follow-up	QTc Prolongation (ms)			p value
	Yes	No	Total	
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
at baseline (Day 1)	395.17 \pm 9.04	404.45 \pm 12.18	403.90 \pm 12.18	0.070
after 2 days	410.50 \pm 18.60	401.97 \pm 11.28	402.47 \pm 11.87	0.088
after 3 days	401.33 \pm 15.42	403.04 \pm 11.87	402.94 \pm 12.02	0.737
after 4 days	406.67 \pm 13.66	403.63 \pm 12.08	403.80 \pm 12.12	0.554
after 5 days	461.33 \pm 6.25	402.44 \pm 12.89	405.90 \pm 18.77	<0.001

Table-3: Results of QTc Prolongation

QTc Prolongation	Frequency	Percent
Yes	6	5.9
No	96	94.1
Total	102	100.0

Table-4: Stratification results of QTc Prolongation with age and gender

Variables		QTc Prolongation		Total	p value
		Yes	No		
Age Groups	2-5 years	2	43	45	0.155
		33.3%	44.8%	44.1%	
	6-10 years	4	30	34	
66.7%		31.3%	33.3%		
11-12 years	0	23	23		
	0.0%	24.0%	22.5%		
Gender	Male	1	45	46	0.149
		16.7%	46.9%	45.1%	
	Female	5	51	56	
83.3%		53.1%	54.9%		

DISCUSSION:

Azithromycin, similar to other macrolides, obstructs IKr potassium channels in cardiac cells, resulting in a delay in ventricular repolarization.

This delay is evident as an elevated QTc interval (the corrected QT interval) on the electrocardiogram (ECG). The QTc interval denotes the duration required for ventricular

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depolarization and repolarization, with an extended QTc heightening the risk of arrhythmias. Nonetheless, the frequency of such effects in children remains ambiguous due to their physiological differences from adults.

Azithromycin is used for treatment in pediatric patients. It has the ability to extend the QT interval. The present study aimed to evaluate the effect of azithromycin on the process of ventricular repolarization in pediatric patients of lower respiratory tract infections, skin & soft tissue infection, and urinary tract infections.

We found the mean value of QTc interval at baseline was 403.90 ± 12.18 ms, after two Days it was 402.47 ± 11.87 ms, after three days it was 402.94 ± 12.02 ms, after four days it was 403.80 ± 12.12 ms, and after five days it was 405.90 ± 18.77 ms. In a study by Magare et al.,⁽¹³⁾ it was found that the mean value of QTc interval at baseline was 416 ± 20 ms and after three week visits, it was 415 ± 21 ms. They concluded that the use of azithromycin, like the findings of this study, was not associated with increased QTc prolongation.

In current study, QTc prolongation was observed in 5.9% patients. Despite the absence of clinical proof, azithromycin is extensively given to individuals who have been confirmed or are believed to have Covid-19. Azithromycin may elevate the risk of fatal arrhythmias linked to QT interval prolongation. The study conducted by Ramireddy et al.⁽⁹⁾ found the QTc prolongation in 12% patients.

We found mean age of patients was 6.88 ± 3.44 years and mean weight was 20.65 ± 10.32 kg with male to female ratio was 1:1.22. The study by Sunkak et al.⁽¹⁴⁾ found mean age of patients as 9.8 ± 5.3 years with male to female ratio was 1:1.14. These results matched with findings of the current study. They also found no impact of azithromycin on the ventricular repolarization parameters on the electrocardiogram (ECG).

Enhos et al.⁽¹⁵⁾ reported azithromycin usage in children due to its anti-inflammatory and immunomodulatory action but its prophylactic use in children resulted in a modest increase in the QTc interval. Nevertheless, all alterations in the QTc interval were within the safe range in their study. Significantly, it is important to conduct a one-month follow-up treatment to specifically assess for any changes in the QTc interval. Prophylactic

administration of azithromycin can be safely initiated if there is no evidence of prolonged QTc interval duration within the first month.

Assessing safety of azithromycin is important as the many studies in pediatric cohort offers crucial assurance against any significant risk of QTc prolongation from long-term azithromycin usage. Early pediatric trial lasting fewer than 6 months provides prior evidence of cardiovascular safety.⁽¹⁶⁾ Contemporary observational studies including children who are on azithromycin also provide evidence for the safety of azithromycin when used for shorter periods of treatment.^(17, 18)

Our study has few limitations as the study duration was short with limited sample size. Therefore, we suggest that to confirm and broaden our results, a similar study should be carried out in multicenter environments with a larger sample size to get further understanding of the association between azithromycin and QTc interval in children.

CONCLUSION:

We concluded that there was no statistically significant effect of azithromycin on the ventricular repolarization parameters (TQc) on electrocardiogram (ECG) in pediatric patients of lower respiratory tract infections, skin & soft tissue infection, and urinary tract infections treated with azithromycin. This prospective observational study suggests that azithromycin can cause a mild and temporary prolongation of the QTc interval in children, but the risk of severe arrhythmias remains low. Careful consideration should be given to high-risk pediatric patients, and monitoring may be warranted in certain cases.

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