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ORIGINAL ARTICLE

Effects of azithromycin on ventricular repolarization in children with COVID-19

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Abstract
Introduction: Azithromycin is used to treat pediatric COVID-19 patients. It can also prolong the QT interval in adults. This study assessed the effects of azithromycin on ventricular repolarization in children with COVID-19.
Method: The study prospectively enrolled children with COVID-19 who received azithromycin between July and August 2020. An electrocardiogram was performed before, one, three, and five days post-treatment. Using ImageJ®, the following parameters were measured: QT max, QT min, Tp-e max, and Tp-e min. The parameters QTc max, QTc min, Tp-ec max, Tp-ec min, QTcd, Tp-ecd, and the QTc/Tp-ec ratio were calculated using Bazett's formula.
Results: The study included 105 pediatric patients (mean age 9.8±5.3 years). The pretreatment heart rate was higher than after treatment (before 92 [79–108]/min vs. Day 1 82 [69–108)]/min vs. Day 3 80 [68–92.2]/min vs. Day 5 81 [70–92]/min; p=0.05).
Conclusion: Azithromycin does not affect the ventricular repolarization parameters on ECG in pediatric COVID-19 cases.

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PALAVRAS-CHAVE
Azitromicina;
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COVID-19;
Pediatria

Efeitos da azitromicina na repolarização ventricular em crianças com Covid-19

Resumo
Introdução: A azitromicina (AZ) é utilizada no tratamento da COVID-19 em pediatria. Como este fármaco pode prolongar o intervalo QT nos adultos, este estudo avaliou os efeitos da AZ na repolarização ventricular de crianças com COVID-19.
Método: Este estudo prospetivo incluiu crianças com COVID-19 que foram tratadas com AZ em julho-agosto 2020. Foi efetuado um eletrocardiograma (ECG) antes e um, 3 e 5 dias após o tratamento. Utilizando ImageJ ®, foram medidos os parâmetros seguintes: QT max, QT min, Tp-e max, e Tp-e min. Os parâmetros QTc min, Tp-ec max, Tp-ec min, QTcd, Tp-ecd e QTc/Tp-ec *ratio* foram calculados utilizando a fórmula Bazett.
Resultados: O estudo incluiu 105 doentes pediátricos (idade média 9,8±5,3 anos). A frequência cardíaca no pré-tratamento foi mais elevada do que após o tratamento (antes 92 [79–108]/min *versus* dia 1 82 [69–108)]/min *versus* dia 3 80 [68–92,2]/min *versus* dia 5 81 [70–92]/min; p=0,05).
Conclusão: A AZ não afeta os parâmetros de repolarização ventricular no ECG nos casos pediátricos da COVID-19.

Introduction

Azithromycin is a broad-spectrum macrolide antibiotic that has come to the fore for the treatment of COVID-19 due to its antiviral and anti-inflammatory effects.[1,2] Schwartz et al. reported that the use of azithromycin alone is effective early in the disease.[3] Although reports have demonstrated the opposite later in the pandemic, it may be effective in combination with hydroxychloroquine.[4,5]

The antiviral effect of azithromycin is due to its intracellular alkalizing effect. Upon entering endosomal vesicles and lysosomes, azithromycin turns the acidic environment basic, which inhibits endocytosis and replication of the SARS-CoV-2 virus, as the viral envelope also requires an acidic environment. Azithromycin is considered beneficial in COVID-19 treatment via these mechanisms.[6]

In adults, azithromycin can cause sudden cardiac death by triggering torsades de pointes and other ventricular arrhythmias.[7–9] Azithromycin prolongs ventricular repolarization by affecting the myocyte action potential and predisposes to malignant arrhythmias.[10] Ventricular repolarization is seen on an electrocardiogram (ECG) as the QT interval. Although the QT interval is a good indicator of ventricular repolarization, torsades de pointes and sudden cardiac death have been reported without QT prolongation.[11] The Tp-e interval and QTc dispersion also reflect ventricular repolarization and may be more useful at predicting torsades de pointes and other malignant arrhythmias than the QT interval.[12,13] Azithromycin, including long-term prophylactic use, has not been reported to cause malignant ventricular arrhythmias in pediatric patients. However, there is limited evidence that it affects ventricular repolarization in the ECG. We hypothesized that the use of azithromycin alone does not affect ventricular repolarization in children with COVID-19 and it can be used safely in terms of cardiac side effects.

Method

This prospective study enrolled children with COVID-19 hospitalized at Kayseri City Hospital Pediatric Infection Clinic who received oral azithromycin between June and August 2020. The study was approved by the local ethics committee. Informed consent was obtained from the patients and their families. Azithromycin was given as 10 mg/kg orally (maximum 500 mg) on Day 1, followed by 5 mg/kg (maximum 250 mg) on Days 2–5 once daily. A 12-lead ECG was obtained before and on days 1, 3, and 5 of treatment. Patients who did not have at least one ECG before and after the treatment and whose QT and Tp-e intervals could not be calculated due to an excessively parasitic ECG were excluded from the study. The ECG was obtained using a GE Mac 2000® device with a paper speed of 25 mm/s, 10 mv/mm amplitude standard. ECGs were scanned and transferred to a computer in JPEG format. The QT and Tp-e intervals were measured by a pediatric cardiologist using the ImageJ® program.

RR interval: Interval between two consecutive R waves.

QT interval: Interval between the starting point of the QRS complex and the end point of the T wave (End point of the T wave: Crossing point of the terminal limb of the T wave with the isoelectric baseline).

The maximum QT (QT_{max}): The longest QT interval.

The minimum QT (QT_{min}): The shortest QT interval.

Corrected QT_{max} (QTc_{max}) and corrected QT_{min} (QTc_{min}): Corrected QT_{max} and QT_{min} according to heart rate using Bazett's formula.

Bazett's formula: $QTc=QT/(RR)^{1/2}$.

QTc dispersion (QTcd): Difference between QTc_{max} and QTc_{min}.

The T wave peak to T wave end interval (Tp-e): Interval between the peak of the T wave and the end of the T wave. (T wave peak: the point at which T wave had highest amplitude, T wave end: the crossing point of T wave with isoelectric line).

Table 1 Demographic and laboratory parameters.

Age (years) (n=105)	9.8±5.3
Gender (F/M)	56/49
Length of stay (day)	7.05±3.0
Creatine kinase (U/L) (n=51)	88 (62–137)
CK-MB (U/L) (n=35)	24 (19–33)
Troponin T (ng/L) (n=21)	0.37±0.87
Calcium (mmol/L)(n=95)	9.6±0.5
Potassium (mmol/L) (n=81)	4.3±0.35
Magnesium (mmol/L) (n= 35)	2.0±0.18

F/M: female/male; CK-MB: creatine kinase myocardial band.

Corrected Tp-e (Tp-ec): Corrected Tp-e according to heart rate using the Bazett's formula.

Maximum Tp-e (Tp-e_{max}) and the minimum Tp-e (Tp-e_{min}) intervals: The longest and the shortest Tp-e intervals.

Tp-ec dispersion (Tp-ed): Difference between Tp-ec_{max} and Tp-ec_{min}.[14]

Statistical analysis

The normality of the distribution of the ECG measurements and ratios were determined using the Kolmogorov–Smirnov test. Descriptive statistics are expressed as the mean ± standard deviation (SD) for continuous variables and proportion for categorical variables. The Friedman test was used to assess repeat ECG measurements before and after treatment. A $p<0.05$ was considered statistically significant. All statistical analyses were conducted with the Statistical Package for the Social Sciences for Windows ver. 22.0 (SPSS, Chicago, IL, USA).

Results

The study included 105 pediatric patients who were hospitalized with a positive COVID-19 PCR test and treated with oral azithromycin. Mean hospital stay was 7.05±3.0 days; mean age was 9.8±5.3 years and the female/male ratio was 56/49 (Table 1). Serum levels of calcium, potassium, and magnesium were normal before treatment. No elevated creatine kinase (CK), CK-MB, or troponin levels were detected (Table 1).

While 30 patients had at least one symptom of COVID-19, 75 were asymptomatic and were diagnosed after in-family transmission. In all, 16 patients had a fever, 10 had a cough, four had joint pain, three had sore throats, two had shortness of breath, abdominal pain, and diarrhea, and 1 each had anorexia and loss of taste and smell. At least one chest X-ray was obtained for all patients and six were classified as infiltrative by a pediatric radiologist. Computed tomography was performed in 22 patients and 9 were evaluated as infiltrative. In addition to azithromycin, two patients received hydroxychlorine and one received favipiravir. There was no significant QTc prolongation in these patients after treatment, but due to the small number of patients, no separate group was assessed statistically.

Of the patients who had at least one ECG before and after treatment, 105 had an ECG before treatment, and 85, 45, and 72 patients had one on days 1, 3, and 5 of treatment, respectively. ECGs could not be obtained routinely due to the risk of contamination and the frequent changes of nurses.

Heart rate was higher before treatment than on the other days (before treatment 92 (79–108)/min vs. Day 1 82 (69–108)/min vs. Day 3 80 (68–92.2)/min vs. Day 5 81 (70–92)/min; $p<0.001$). Before treatment, QT_{max} was shorter than the Day 5 measurement due to the high heart rate (328 (306–362) vs. 347.5 ms (320–368.5); $p=0.005$). QT_{min} was shorter before treatment than on days one and five of treatment (before 305 (281.5–335) ms vs. Day 1 312 (285–340) ms vs. Day 5 323 (300.2–345.7) ms; $p=0.03$–0.004). QTc_{max} and QTc_{min} were similar before and after treatment, after correction for heart rate using Bazett's formula.

Before treatment, the QTc_{max} of five patients exceeded 450 ms. The highest QTc was 466 ms. These patients had QTc_{min} intervals <450 ms, no family history of sudden death or prolonged QT syndrome, and there was no significant prolongation of QTc during treatment. QTcd was similar on days 1, 3, and 5 compared to before treatment ($p>0.05$) (Table 2).

Tp-e_{max} and Tp-e_{min} were similar before and after treatment (Table 2) ($p>0.05$). No QT_{max} or QT_{min} shortening due to a high heart rate was observed in Tp-e_{max} and Tp-e_{min}. Before and after treatment, Tp-ec_{max} and Tp-ec_{min} were similar. No difference was observed in Tp-ec dispersion before and after treatment ($p>0.05$), nor were there differences in Tp-ec_{max}/QTc_{max} and Tp-ec_{min}/QTc_{min} ratios before and after treatment (table 2) ($p>0.05$).

Discussion

COVID-19 was first reported in Wuhan, China, and later caused a global pandemic.[15] Although COVID-19 is not as severe in children as in adults, it can still cause pneumonia and death.[16,17] Therefore, asymptomatic or mildly symptomatic patients need treatment.[2,18]

In this study, oral azithromycin had no effect on QTc, Tp-ec, QTc, or Tp-ec dispersion or the Tp-ec/QTc ratio in children with COVİD-19. Azithromycin is a broad-spectrum macrolide antibiotic with broad pediatric indications (respiratory, genitourinary, and enteric bacterial infections). Its antiviral and anti-inflammatory effects have made it an alternative treatment for COVİD-19.[2,19]

The antiviral effects of azithromycin are not fully understood and are thought to be due to many different mechanisms. In human cells, endosome maturation and function require an acidic environment. Azithromycin is a basic molecule that accumulates intracellularly in endosomal vesicles and lysosomes, thus making the environment basic. In this way, it prevents viral replication by blocking viral endocytosis or viral genetic shedding from lysosomes.[20–22] Similar to influenza and human immunodeficiency viruses, the SARS-COV-2 viral envelope requires an acidic environment and the basic nature of azithromycin prevents enveloping and reduces viral replication.[22]

For COVID-19, azithromycin is often used in combination with hydroxychloroquine. However, there are few reports on its use in pediatric patients.[3,23,24] Hydroxychloroquine prolongs the QT interval and causes torsades de pointes and other fatal arrhythmias; we use AZ in asymptomatic

Table 2 Electrocardiogram parameters and calculations.

	Before treatment (n=105)	1st day (n=85)	3rd day (n=45)	5th day (n=72)	p value
Heart rate (/min)	92 (79–108)	82 (69–108)	80.5 (68–92.2)	81 (70–92)	<0.001 (1.3.5)
QTmax, ms	328 (306–362)	337 (308.5–365)	353 (331–372)	347.5 (320–368.5)	0.005 (5)
QTmin, ms	305 (281.5–335)	312 (285–340)	329 (310–351.5)	323 (300.2–345.7)	0.03–0.004 (1–5)
QTcmax, ms	404.5 (384.1–424.3)	406.2 (381.2–423.0)	405.1 (376.4–416.6)	398.7 (376.3–415.6)	0.101
QTcmin, ms	375.6 (360.4–392.9)	377.5 (355.3–389.6)	377 (356.2–391.7)	376.4 (352.8–386.6)	0.084
QTcd, ms	31.0 (18.9–39)	28.4 (21.1–39.2)	23.4 (16.9–35.4)	23.8 (16.2–31.1)	0.056
Tp-emax, ms	85 (75–95)	83 (76–95)	83 (78–90)	80 (73–95)	0.670
Tp-emin, ms	60 (54–70)	60 (52–66.5)	65 (54.5–70.5)	60 (55–66)	0.675
Tp-ecmax, ms	102.1 (91.5–120.3)	99.2 (85.9–114.6)	95.3 (86–106.2)	95.7 (84.5–106.1)	0.176
Tp-ecmin, ms	75.7 (67.1–85.2)	70 (63.1–79.4)	72.6 (63.2–84.7)	70.1 (62–80.2)	0.271
Tp-ecd, ms	25.4 (18.0–37.3)	26.8 (18.2–37.6)	22.9 (16.7–28.8)	23.2 (15.5–29.7)	0.097
Tp-ecmax/QTcmax	0.25 (0.22–0.29)	0.25 (0.21–0.28)	0.24 (0.22–0.25)	0.23 (0.21–0.26)	0.843
Tp-ecmin/QTcmin	0.20 (0.18–0.22)	0.19 (0.17–0.21)	0.19 80.16–0.22)	0.18 (0.16–0.20)	0.383

QTmax: maximum QT interval; QTmin: minimum QT interval; QTcmax: Corrected maximum QT interval; QTcmin: Corrected minimum QT interval; QTcd: QTc dispersion (QTcmax–QTcmin); Tp-emax: Maximum T-peak to T-end interval; Tp-emin: Minimum T-peak to T-end interval; Tp-ecmax: Corrected Tp-emax; Tp-ecmin: Corrected Tp-emin; Tp-ecd: Tp-ec dispersion (Tp-ecmax-Tp-ecmin); ms: milliseconds.

or mildly symptomatic patients. Of our patients, 71% were asymptomatic and the others had mild symptoms. Therefore, we preferred azithromycin over hydroxychloroquine due to its less arrhythmogenic effect, although some studies from later in the pandemic reported that it was not effective clinically.[4,5]

In clinical practice, many drugs cause long QT syndrome and torsades de pointes. In drug-induced long QT, the depolarizing currents increase or repolarizing currents decrease. As a result, the repolarization time of the ventricular action potential is prolonged, which manifests as QT interval prolongation on an ECG.[25,26] Azithromycin causes this by increasing the intracellular cardiac sodium flow and supporting sodium overload.[27] The prolongation of the action potential predisposes the patient to torsades de pointes and other malignant arrhythmias. No studies have assessed the use of azithromycin alone on cardiac arrhythmias in patients with COVID-19. However, when used in combination with hydroxychloroquine, it prolongs the QTc more than when using hydroxychloroquine in monotherapy.[27,28]

Many ECG parameters are used to assess the susceptibility to torsades de pointes and other malignant arrhythmias with certain drugs. The most commonly used are the QT interval and QTc, the corrected QT interval for heart rate with Bazett's formula. The American College of Cardiology considers a QTc >480 ms for women and >470 ms for men as being pathological.[26]

In many drug-induced arrhythmias, slow potassium channels are affected by the rapid delayed rectifier K^+ current, which manifests as prolongation of the QT interval in ECG and torsades de pointes.[29] However, cardiac repolarization is complex and many ion channels are active. Genetic and disease-related acquired mechanisms may also prolong the QT interval. In other words, torsades de pointes can occur without prolongation of the QT interval.[30]

In our study, heart rate was higher before treatment than after, because of anxiety due to hospitalization and fever before treatment (16 patients had fevers). This increase in heart rate did not persist over subsequent days. The QT interval was shorter before azithromycin treatment than on the other days. However, after correcting for heart rate with Bazett's formula, there were no differences in QTc before and after treatment. Choi et al. found that old age was a risk factor for QT prolongation due to azithromycin treatment, and the risk decreased with age.[31] Another risk factor is a low heart rate.[32,33] The QTc interval is less prolonged due to drugs in pediatric patients who already have high heart rates. We did not find any evidence in the literature that azithromycin treatment alone prolongs QTc and causes torsades de pointes in pediatric patients. Although Murphy et al. found that QTc was longer in pediatric patients given azithromycin for obsessive compulsive disorder than in those given placebo, it did not exceed 460 ms in any patient.[34] There are reports that QT is not prolonged with long-term

prophylactic azithromycin. Moreno et al. reported on the administration of long-term azithromycin in 86 patients and found that there was no QTc prolongation.[35] Magaret et al. administered azithromycin to 221 patients with cystic fibrosis for between three weeks and 18 months and none had a QTc>500 ms.[36] Another reason why there was no change in QTc in our patients was the absence of significant inflammation, which can itself prolong the QT interval.[37,38] Furthermore, our patients were not given any other treatment that could impair ventricular repolarization. We did not include patients who received hydroxychloroquine and favipiravir in our study.

QTc dispersion (QTcd) is defined as the difference between QTc_{max} and QTc_{min}. Its prolongation is a risk factor for malignant arrhythmias and sudden cardiac death in both congenital and drug-induced long QT syndrome.[39–41] However, its normal value varies across studies. Elming et al. reported that QTd>90 ms increases the risk of malignant arrhythmias.[42] While Yenercag et al. did not find a difference in QTd in COVID-19-positive adults compared to controls.[43] We found no differences in QTd before and after treatment in our study group.

Transmural dispersion of repolarization is a predictor of torsades de pointes. In isolated ventricular wedge studies, the peak of the T wave coincides with epicardial repolarization and the end of the T wave with the repolarization of M cells. Therefore, the Tp-e interval and dispersion measure the transmural dispersion of repolarization. The Tp-e/QTc ratio is more useful than the QT interval for predicting torsades de pointes and other malignant arrhythmias.[44,45] We measured the Tp-e interval and corrected it for heart rate with Bazett's formula; there were no differences in the Tp-ec interval and Tp-ec/QTc ratio before and after treatment. We did not find any study that has assessed azithromycin treatment using the Tp-e interval and Tp-ec/QTc ratio in children with either COVID-19 infection or other indications.

Increased CK, CK-MB, and troponin levels have been reported in COVID-19-positive patients. However, these cardiac markers were normal in our series.

Study limitations

Azithromycin could not be compared to the combination of azithromycin+hydroxychloroquine. Arrhythmogenic side effects may be obvious with combination therapies. Our patients did not have severe COVID-19 and inflammation may increase this possible effect of azithromycin treatment. Therefore, further studies of patients with severe COVİD-19 and comparison with combination therapies are needed.

Conclusion

Oral azithromycin treatment alone did not affect ventricular repolarization in children with COVID-19. In terms of cardiac side effects, azithromycin appears to be safe in asymptomatic or mildly symptomatic pediatric patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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