

Assessment of Short-term Electrocardiographic Changes Induced by Antibiotic Amoxicillin and Clavulanate

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Abstract

Background and Objectives: Antibiotics are widely used for variety of infections. Drugs like Macrolides, Flouroquinolones can cause prolongation of the QT interval. The objective of this study was to assess the changes in 12 lead Electrocardiogram of patients receiving intravenous Amoxicillin and Clavulanate, parameters like heart rate and corrected QT interval (QTc) were analyzed. *Methods:* A total of 40 patients who received intravenous Amoxicillin and Clavulanate were enrolled in the study. Serial 12 lead surface Electrocardiogram were taken at 4 time points as follows. First ECG taken before the administration of the antibiotic. These were followed by a 10 minutes, 20 minutes and 60 minutes of infusion. The parameters of Electrocardiogram viz; Heart rate, QTc Interval were assessed. *Results:* In our study we found that there was mean increase in the heart rate of less than 2 beats per minute and mean increase in QTc interval of 9.6 ms at 60 minutes when compared to baseline. This difference was statistically significant but clinically not significant as the corrected QT interval was still within the normal range. *Conclusion:* Administration of antibiotics like Amoxicillin and Clavulanate, through intravenous route caused a minimal though statistically significant increase in heart rate and QTc at 60 minutes compared to baseline, in patients without cardiovascular disease or electrolyte disturbances. However the corrected QT intervals remained in the normal range. These results point to the need for further studies in larger groups of patients including those with cardiovascular disease and other comorbidities.

Keywords: Antibiotic; Amoxicillin and clavulanate; ECG; Heart rate; QTc.

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Introduction

Cardiac toxicity can occur as an unintended consequence of drug therapy and is considered to

be an increasingly important, but rare, medication-related adverse event. In the United States alone, between 300,000 and 400,000 people die annually of sudden cardiac death.¹ Torsades de pointes

(TdP), a potentially fatal polymorphic ventricular tachyarrhythmia, often occurs in association with a prolonged QT interval or a heart-rate-corrected QT interval (QTc) and it may present as sudden death.

The QT interval is the interval from the beginning of the QRS complex to the end of the T wave, The QT interval encompasses both the depolarization phase and the repolarization phase of the action potential. The QT interval is also modulated by an individual's heart rate, autonomic tone, sex, and age.² Methods to correct for some of the variability inherent in QT interval chiefly, heart rate do exist. Several correction formulas are used, including the Bazett and Fridericia formulas.^{3,4}

Amoxicillin is an aminopenicillin which is an extended spectrum penicillin and Clavulanate is a beta lactamase inhibitor. This combination covers both gram positive and gram negative bacteria

The objective of this study was to assess the changes at 3 time points in the resting 12 lead Electrocardiogram of patients following administration of Amoxicillin and Clavulanate. Parameters like heart rate and corrected QT interval (QTc) were analyzed.

Materials and Methods

Study Design is a descriptive study, after ethical committee approval and informed consent total of 40 patients chosen who are on Amoxicillin and Clavulanate. Serial 12 lead surface Electrocardiogram were taken using BPL Caridart 6208 view machine related input voltage AC 220V-240V/100V-115V; DC 14.8V, related frequency 50 Hz/60 Hz) and are as follows. 1st before the administration of the antibiotic. 2nd after 10 minutes of infusion. 3rd after 20 minutes of infusion. 4th after 60 minutes of infusion. The parameters of electrocardiogram viz; heart rate, QTc interval were assessed and recorded. QTc was calculated using Bazett's Formula, i.e. $QTc = QT / \sqrt{RR}$ interval.

The parameters heart rate, QTc were analyzed using repeated ANOVA (Analysis of variance)

measures. Variables in rate were defined as R0 as baseline heart rate, R10, R20, R60 as 10th minute, 20th minute and 60th minute heart rate respectively. In the same manner QTc was also named as QTc0 for baseline QTc value, QTc10, QTc20, QTc60 for 10th minute, 20th minute and 60th minute corrected QT interval value respectively. I time is baseline ECG measurement for either heart rate or QTc and J time is measurement at different intervals viz; 10th, 20th and 60th minute for 2, 3 and 4 respectively

Inclusion Criteria

- Be 18-years-old or older.
- Patients who was started on any of the chosen antibiotic

Exclusion Criteria

- Patients with hypokalemia
- Patients with hypothermia
- Patients with hypocalcaemia
- Patients on drugs like Tricyclic antidepressants, Quinidine
- Existing cardiovascular disease

Statistical Analysis

Repeated measures ANOVA was used to compare change in heart rate and QTc intervals electrocardiogram parameters across 0 minute, 10 minutes, 20 minutes and 60 minutes. *p* value < 0.05 considered statistically significant.

Results

Demographic data

The table 1 provides the Demographic data.

Effect of Amoxicillin-Clavulanate

The Table 2 provides the mean and SD for Rate after amoxicillin and clavulanate administration, the mean increase from baseline to 60th minute was less than 2 beats per minute.

Table 1: Demographic data

Characteristic		Total No.	%
Gender	Male	24	60
	Female	16	40
Age:	20-39 years	12	30
	40-59 years	16	40
	>60	12	30

We can report that when using an ANOVA with repeated measures with a Greenhouse-Geisser correction, the mean scores for Rate concentration were statistically significantly different. The results

presented in the Table 2 informed us that we have an overall significant difference in means, but we do not know where those differences occurred.

Table 2: Changes in heart rate after administration of Amoxicillin-clavulanate

Descriptive Statistics			
	Mean	Std. Deviation	N
R0	78.95	10.917	40
R10	79.30	10.343	40
R20	79.95	9.886	40
R60	81.05	9.693	40

Pairwise Comparisons Measure: Heart Rate

Table 3 presents the results of the Bonferroni post hoc test, which allows us to discover which specific means differed.

Table 3 gives us the significance level for differences between the individual time points. We can see that there was a statistically significant but not clinically significant difference in rate concentration between

Table 3: Pairwise comparison of heart rate after administration of Amoxicillin-clavulanate

Pairwise Comparisons Measure: Heart Rate						
(I) Factor 1	(J) Factor 1	Mean difference (I-J)	Std. Error	Sig. ^b	95% Confidence interval for difference ^b	
					Lower bound	Upper bound
1	2	0.350	0.201	0.538	0.209	0.909
	3	1.000*	0.351	0.042	0.025	1.975
	4	2.100*	0.303	<.001	1.257	2.943

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Test used: Bonferroni post hoc test

baseline and 20th min of 1 per minute ($p = 0.042$, 95% confidence interval. 025–1.975) and between baseline and 60th minis of 2 beats per minute (p -value < 0.001, 95% confidence interval 1.257–2.943).

Effects on corrected QT interval after administration of Amoxicillin - Clavulanate

The Table 4 provides the mean and SD for corrected QT interval for amoxicillin clavulanate

Table 4: Effects on corrected QT interval after administration of Amoxicillin-clavulanate

Descriptive statistics			
	Mean	Std. deviation	N
QTc0	393.85	18.388	40
QTc10	395.55	17.142	40
QTc20	400.35	16.818	40
QTc60	403.50	16.921	40

Table 5: Changes in corrected QT interval after administration of amoxicillin-clavulanate

Estimates				
Measure: QTC				
Factor1	Mean	Std. Error	95% Confidence interval	
			Lower bound	Upper bound
1	393.850	2.907	387.969	399.731
2	395.550	2.710	390.068	401.032
3	400.350	2.659	394.971	405.729
4	403.500	2.675	398.089	408.911

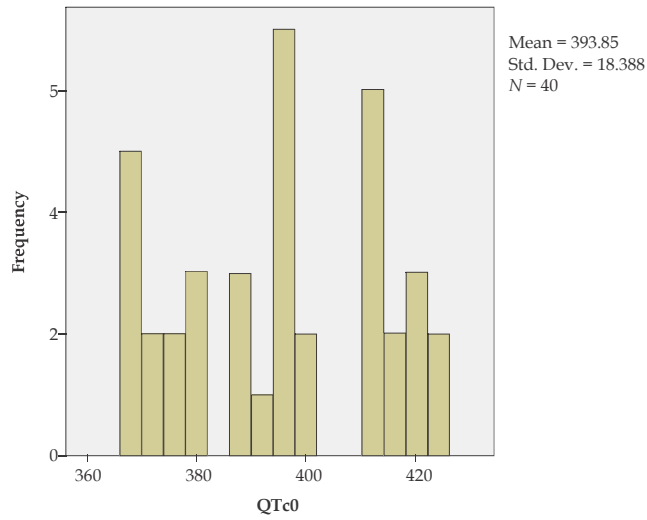


Fig. 1a:

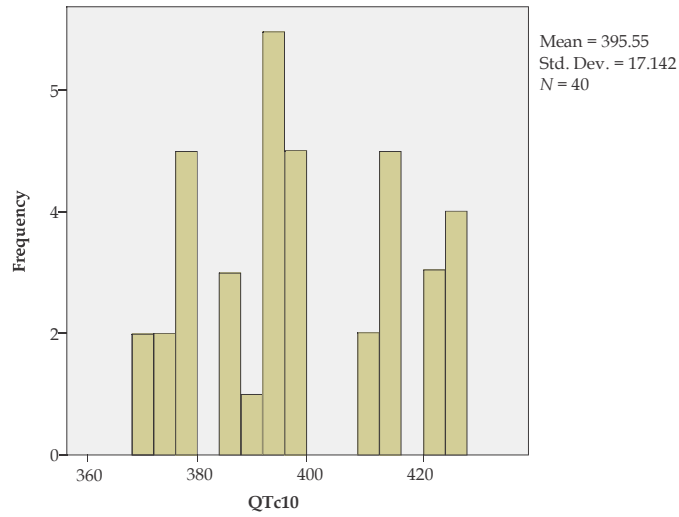


Fig. 1b:

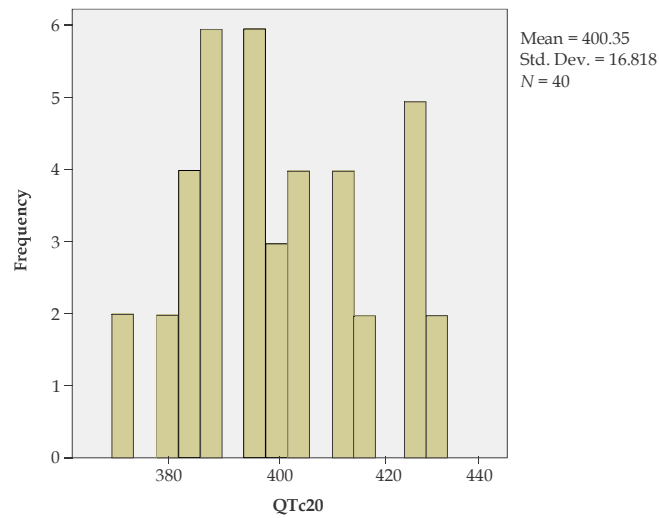


Fig. 1c:

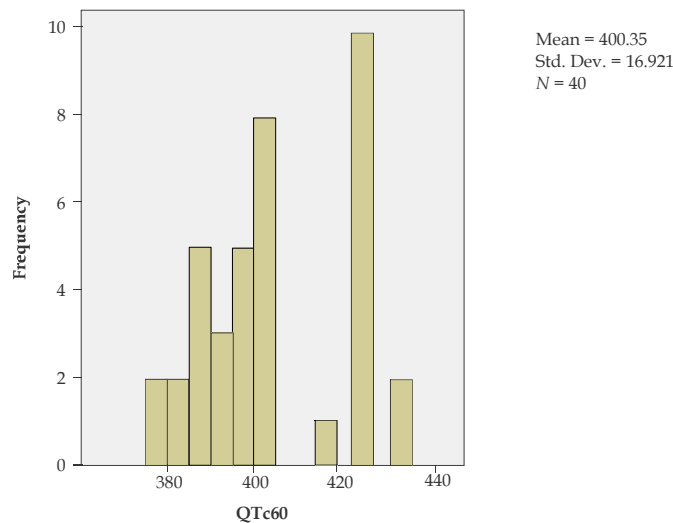


Fig. 1d:

Figs. 1a,b,c,d: Provides information regarding histogram representation of corrected QT interval after administration of amoxicillin clavulanate.

group, the mean increase of QTc from baseline to 60th minute was 9.6 ms which was statistically significant but clinically not. We can report that when using an ANOVA with repeated measures with a Greenhouse-Geisser correction, the mean scores for QTc2 concentration were statistically significantly different (Fig. 4).

Changes in corrected QT interval after administration of amoxicillin-clavulanate

Table 5 provides information regarding mean value of corrected QT interval of amoxicillin clavulanate group.

Table 6: Pairwise comparison of corrected QT interval after administration of Amoxicillin-clavulanate

Measure		Pairwise Comparisons					
(I) Factor 1	(J) Factor 1	Mean difference (J-I)	Std. Error	Sig. ^b	95% Confidence interval for difference ^b		
				Lower bound			Upper bound
1	2	1.700	1.149	0.883	1.494	4.894	
	3	6.500*	1.448	0.001	2.476	10.524	
	4	9.650*	1.379	0.001	5.817	13.483	

Based on estimated marginal means
 *. The mean difference is significant at the .05 level.
 b. Adjustment for multiple comparisons: Bonferroni.
 Test Used: Bonferroni post hoc test

Pairwise comparison of corrected QT interval after administration of Amoxicillin-clavulanate

The results presented in the Table 6 informed us that we have an overall significant difference in means, but we do not know where those differences occurred. Table 6 presents the results of the Bonferroni post hoc test, which allows us to discover which specific means differed. Table 6 gives us the significance level for differences between the individual time points. We can see that there was a significant difference in QTc2 concentration between baseline and 20th min, the mean increase was 6.5 ms (*p*-value <0.001, 95%

confidence interval 2.476-10.524) and between baseline and 60th min, the mean increase was 9.6 ms (*p*-value <0.001, 95% confidence interval 5.817 -13.483).

Discussion

Corrected QT interval values according the committee for proprietary medicinal products defined normal value of QTc in males <430 ms and in females <450 ms, it is said to be prolonged if >450 ms in adult males and >470 ms in adult females. None of our patients had prolonged QTc and none

of our patients developed arrhythmia during the study. Analysis of mean increase of corrected QT interval in Amoxicillin and Clavulanate antibiotic was done which showed a statistically significant but not clinically significant, difference of less than 2 ms in QTc concentration between baseline and 60th minute of 9.6 ms increase ($p = <0.05$, 95% confidence interval 5.817–13.483) (Tables 7-10).

Distribution of subjects in various studies

Table 7: Distribution of subjects in various studies

Study	Subjects
Our study	40
Basyigit et al. ⁵	26
Strle et al. ⁶	47
Makaryus et al. ⁷	38

Distribution of age in various studies

Table 8: Distribution of age in various studies

Study	Age in years
Our study	27–76
Basyigit et al. ⁵	29–73
Strle et al. ⁶	19–77
Makaryus et al. ⁷	46–84

Effect on heart rate in different study groups

Table 9: Distribution of age in various studies effect on heart rate in different study groups

Study	Drug used	Effect on heart rate
Our study	Amoxicillin and Clavulanate	Mean increase of less than 2 beats per minute
Basyigit et al. ⁵	Levofloxacin	Mean increase of 4 beats per minute
Mishra et al. ⁸	Erythromycin	Mean increase of 4 beats per minute

Effect on corrected QT interval

Table 10: Effect on heart rate in various studies effect on corrected QT interval

Study	Drug used	Effect on corrected QT interval
Our study	Amoxicillin and Clavulanate	Mean increase of about 9.6 ms
Basyigit et al. ⁵	Levofloxacin	Mean increase of 13 ms
Mishra et al. ⁸	Erythromycin	Mean increase of 4 ms
Tsikouris et al. ⁹	Ciprofloxacin, Levofloxacin, Moxifloxacin	Mean increase of 7 ms

Conclusion

Administration of antibiotic Amoxicillin and Clavulanate through intravenous route caused a minimal though statistically significant increase in heart rate and QTc at 60 minutes compared to baseline, in patients without cardiovascular disease or electrolyte disturbances. However the corrected QT intervals remained in the normal range. These results point to the need for further studies in larger groups of patients including those with cardiovascular disease and other comorbidities.

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