# QT Interval Prolongation Associated with Amiodarone Use in Cipto Mangunkusumo Hospital, Jakarta

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## ABSTRAK

***Tujuan:*** *mempelajari kejadian perpanjangan interval QTc pada pemakaian amiodaron di RSCM dan faktor yang mempengaruhinya.* ***Metode:*** *penelitian deskriptif retrospektif dilakukan berdasarkan rekam medik pasien yang dirawat di ICCU RSCM tahun 2004-2011. Penelitian dilakukan pada 4 kelompok pasien yaitu (1) kelompok yang menggunakan amiodaron dan obat lain yang menyebabkan perpanjangan interval QTc; (2) kelompok yang menggunakan amiodaron dengan obat-obat lain yang tidak menyebabkan perpanjangan interval QTc; (3) kelompok yang menggunakan obat selain amiodaron yang memperpanjang interval QTc dan (4) kelompok kontrol (tidak menggunakan amiodaron atau obat lain yang memperpanjang interval QTc). Perubahan interval QTc (ΔQTc) selama perawatan dalam satu kelompok dianalisis dengan uji t berpasangan atau Wilcoxon. Perbandingan ΔQTc antar kelompok dianalisis dengan uji Kruskal Wallis. Pengaruh faktor lain (jenis kelamin, umur, gagal jantung, fungsi hati dan elektrolit) terhadap kejadian perpanjangan interval QTc dianalisis dengan menggunakan regresi multipel.* ***Hasil:*** *perpanjangan interval QTc pada kelompok 1, 2, dan 3 secara berturut-turut adalah 65,5%, 63,3%, 56,6% yang berbeda bermakna dibandingkan kelompok kontrol (24,4%, p <0,05). Tidak terdapat potensiasi perpanjangan interval QTc bila amiodaron dikombinasi dengan obat lain yang menyebabkan perpanjangan QT. Hipernatremia dan hipertensi merupakan faktor risiko terjadinya perpanjangan interval QTc. Terdapat kematian pada kelompok 1, 2, dan 3 masing-masing 3, 4, dan 4 pasien, sedangkan pada kelompok 4 tidak terdapat kematian.* ***Kesimpulan:*** *perpanjangan interval QTc secara bermakna terjadi pada pemakaian amiodaron dan beberapa obat yang menyebabkan perpanjangan interval QT, namun tidak terjadi potensiasi bila kedua kelompok obat digunakan bersamaan. Hipernatremia dan hipertensi memberikan kontribusi pada perpanjangan interval QTc.*

***Kata kunci:*** *amiodaron, anti-aritmia, interval QTc.*

## ABSTRACT

***Aim:*** *to evaluate the incidence of QTc interval prolongation associated with the use of amiodarone, as well as factors that influence its occurrence.* ***Methods:*** *this was a descriptive retrospective study conducted from November 2010 until December 2011 using medical record of patients at ICCU Cipto Mangunkusumo Hospital from 2004-2011. Four groups of patients were included: (1) patients receiving amiodarone and other drugs causing which can cause QTc prolongation, (2) patients receiving amiodarone and other drug not causing QTc prolongation, (3) patients receiving drugs which can cause causing QTc prolongation, (4) patients not receiving amiodarone, nor other drugs which can cause causing QTc prolongation (served as control group). Difference of QTc interval within the same group was analyzed with paired t-test or Wilcoxon matched-pairs test. Between*

*groups comparison were performed with Kruskal Wallis test. The influence of other factors (sex, age, heart failure, liver disorder, electrolyte imbalance) on QTc prolongation was analyzed using multiple regression.* ***Results:*** *QTc interval prolongation in groups 1, 2, and 3 were respectively 65.5%, 63.3%, 56.6%, which were significantly different from control group (24.4%); Hypernatremia and hypertension were revealed as significant risk factor for QTc prolongation. Mortality occurred in 3, 4, and 4 patients in group 1, 2, and 3 respectively, and none in group 4.* ***Conclusion:*** *QTc interval prolongation occurred in association with amiodarone and other drugs known to prolong QTc interval. Hypernatremia and hypertension were shown as significant influencing factor of QTc interval prolongation.*

***Key words:*** *amiodarone, antiarrhythmia, QTc interval.*

## INTRODUCTION

Amiodarone is a wide spectrum antiarrhythmic drug which shows very good activity against various types of arrhythmias including atrial flutter and fibrillation, as well as arrhythmias of ventricular origin. It has a good pharmacologic profile, and represents the most widely used antiarrhythmia.[1] Beside its good pharmacologic profile, amiodarone possesses a potentially dangerous adverse effect, i.e QT interval prolongation which can lead to torsade des pointes or polymorphic ventricular arrhythmia, which may end with ventricular fibrillation and sudden death.[2,3]

QT interval is defined as the time needed by the ventricle to perform complete depolarization and repolarization.[1,2] Some drugs are known to induce QT interval prolongation by inhibiting outward current of potassium ion, which lead to prolongation of myocardial repolarization. Some drugs in the group of antiarrhythmic drugs, antidepressants, antipsychotics such as haloperidol, and some antibiotics such as quinolones, azithromycin, and metronidazole, are known to cause QT interval prolongation.[4-6]

Some patients admitted to intensive cardiac care unit known to have various types of arrhythmia and need antiarrhythmic drugs, including amiodarone. Some of them also received concomitant drugs causing QT interval prolongation. However, publication on the incidence of QT interval prolongation in this group of patients in Indonesia is still lacking. In the present study, we aimed to evaluate the incidence of QTc interval prolongation in patients receiving amiodarone and other drugs which can cause QT prolongation at Intensive Cardiac Care Unit of Cipto Mangunkusumo Hospital, Jakarta. Role of other factors such as gender, electrolyte imbalance, presence of heart failure and liver disorder in the occurrence of QT interval prolongation was also evaluated.

## METHODS

This was a descriptive retrospective study conducted using secondary data from medical record of patients hospitalized in the Intensive Cardiac Care Unit (ICCU) of Cipto Mangunkusumo Hospital, Jakarta during the period of 2004 to 2011. All patients aged between 16-65 years were included in this study, while those with incomplete or unreadable ECG data were excluded. A total of 200 samples were planned, but only 176 samples were eligible for analysis. The protocol of this study has been approved by Research Ethics Committee of the Faculty of Medicine Universitas Indonesia.

The patients were classified into 4 groups according to the drugs they received. Group I received amiodarone and other drugs causing QT prolongation; group II received amodarone and other drug(s) not causing QT prolongation; group III received other drugs causing QT prolongation, without amiodarone; and group IV received neither amiodarone, nor drugs causing QT prolongation. Since QT interval is inversely correlated with heart rate, thus, it is presented as corrected QT interval (QTc). The correction formula used in this study is based on Bazett equation where QTc = QT/(RR).[7]

During this study, QT interval prolongation is defined as QTc more than 450 ms, or the increase of more than 30% from baseline value, and lead II was taken as reference of QT interval calculation.[6]

### Data Analysis

Demographic data as well as laboratory results were reported descriptively. The difference of QTc interval (ΔQTc) between baseline and the longest QTc during hospitalization within one group was analyzed by using paired t-test or Wilcoxon matched-pair test. Percentage of difference between groups were analyzed by using Kruskal Wallis test. Influence of other factors such as gender, age, presence of heart failure, serum electrolyte on QT prolongation was analyzed by multiple regression with backward approach. Mortality in each group was presented descriptively.

## RESULTS

A total of 176 data have been collected comprising of group I (29 patients), II (49 patients), III (53 patients), and IV (45 patients). **Table 1** shows distribution of patients according to gender, age, cardiac diseases, serum electrolyte, and liver function.

**Table 1.** Demographic data and distribution of cardiac diseases, serum electrolyte, and liver dysfunction of study subjects

| Variables | Group | | | | Total n (%) |
|---|---|---|---|---|---|
| | I n (%) | II n (%) | III n (%) | IV n (%) | |
| Gender: | | | | | |
| - Male | 20 (69) | 33 (67) | 33 (62) | 28 (62) | 114 (65) |
| - Female | 9 (31) | 16 (33) | 20 (38) | 17 (38) | 62 (35) |
| Age: | | | | | |
| - Years (SD) | 58 (10) | 51 (12) | 53 (7) | 52 (7) | 53 (9) |
| - Range | 30 - 69 | 25 - 69 | 32-65 | 36-65 | 25-69 |
| Cardiac disease: | | | | | |
| - UAP | 2 (6,8) | 8 (16,3) | 14 (26,4) | 10 (22,2) | 34 (19,3) |
| - NSTEMI | 9 (31) | 6 (12,2) | 17 (32) | 15 (33,3) | 47 (26,7) |
| - STEMI | 11 (37,9) | 18 (36,7) | 16 (30,2) | 15 (33,3) | 60 (34,1) |
| Heart failure: | | | | | |
| - Yes | 18 (62) | 23 (47) | 31 (58) | 9 (20) | 81 (46) |
| - No | 11 (38) | 26 (53) | 22 (42) | 36 (80) | 95 (54) |
| Serum electrolyte: | | | | | |
| - Hypokalemia | 5 (17.2) | 5 (9.4) | 14 (26.34) | 4 (8.9) | 28 (15.9) |
| - Normokalemia | 23 (79.3) | 40 (81.6) | 37 (69.8) | 39 (86.7) | 139 (78.9) |
| - Hypernatremia | 5 (17.2) | 7 (13.2) | 6 (11.3) | 4 (8.9) | 22 (12.5) |
| - Normonatremia | 23 (79.3) | 40 (75.5) | 45 (84.9) | 38 (54.4) | 146 (82.9) |
| Liver function: | | | | | |
| - High SGPT | 3 (10.3) | 5 (10.2) | 5 (9.4) | 5 (11.1) | 18 (10.2) |
| - Normo SGPT | 21 (72.4) | 35 (71.4) | 38 (71.6) | 32 (71.1) | 126 (71.6) |

HF : heart failure, UAP: unstable angina pectoris, NSTEMI: non ST-elevated myocardial infarction, STEMI: ST elevated myocardial infarction

**Table 2** shows baseline QTc interval and prolonged QTc interval of subjects in all groups. A significant increase of QTc interval can be seen in all group. However, the first three groups has about the same magnitude of QTc prolongation, while the group IV which did not received neither amiodarone, nor drug causing prolonged QT, showed a significantly lower QTc prolongation. (**Figure 1**)

Beside the magnitude of QTc prolongation, it can be seen that the proportion of patients having QTc interval prolongation was also significantly lower in group IV (**Table 3**).

**Table 4** shows that azithromycin was the most frequent drug causing prolonged QT received by the subjects. QTc prolongation was

**Table 2.** Comparison of baseline and prolonged values of QTc interval in each group

| | Baseline QTc ms (SD) | Prolonged QTc ms (SD) | p |
|---|---|---|---|
| Group I | 434.8 (57.1) | 478.4 (81.5) | 0.001 |
| Group II | 446.9 (72.4) | 497.6 (108.7) | 0.008 |
| Group III | 464.8 (75.2) | 515.40 (71.7) | 0.001 |
| Group IV | 454.3 (51.1) | 468.4 (55.4) | 0.008 |

**Tabel 3.** Proportion of patients experiencing QTc interval prolongation in the four groups

| | Prolonged QTc n (%) | Normal QTc n (%) | Total N |
|---|---|---|---|
| Group I | 19 (65.5) | 10 (34.5) | 29 |
| Group II | 31 (63.3) | 18 (36.7) | 49 |
| Group III | 30 (56.6) | 23 (43.4) | 53 |
| Group IV | 11 (24.4)* | 34 (75.6) | 45 |
| Total | 91 (51.7) | 85 (48.3) | 176 |

* p<0.05 vs group I, II, III

**Table 4.** Influence of concomitant drug(s) on the occurrence of QTc prolongation

| | Main drug | Concomitant drug (n) | QTc prolongation n (%) |
|---|---|---|---|
| Group I (n = 29) | Amiodarone | Azithromycin (25) | 16 (64) |
| | | Metronidazol (2) | 2 (100) |
| | | Haloperidol (2) | 1 (50) |
| Group II (n = 49) | Amiodarone | - | 31 (63.3) |
| Group III (n =53) | - | Azithromycin (45) | 24 (52) |
| | | Metronidazol (7) | 5 (71) |
| | | Haloperidol (1) | 1 (100) |
| Group IV (n = 45) | - | - | 11 (24.4) |

slightly less in group receiving azithromycin compared with amiodarone or combination of amiodarone and azithromycin, but this different was not significant. Other drugs (metronidazole and haloperidol) are used in much less frequency.

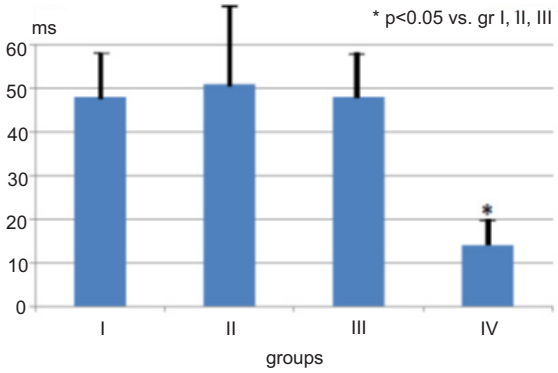


**Figure 1.** Magnitude of changes of QTc interval in all groups during hospitalization at the ICCU

### Influence of Some Risks Factors on the Occurrence of QTc Prolongation

Result of multiple regression shows that among several factors dialyzed, hypernatremia, lung disease, and hypertension have significant influence on the occurrence of QTc interval prolongation (**Table 5**).

**Tabel 5.** Multiple regression of the influence of risks factors on the occurrence of QTc interval prolongation

| Risk factors | B (slope) | p |
|---|---|---|
| Gender | 0,040 | 0.911 |
| Heart failure | 0,201 | 0.569 |
| Hypokalemia | -0,321 | 0.490 |
| Liver disease | 0,358 | 0.488 |
| Hypernatremia | 1,264 | 0.019 |
| Arrhytmia | -0,034 | 0,928 |
| Lung disease | -0,644 | 0,039 |
| Hypertension | 0,830 | 0,009 |

## DISCUSSION

Amiodarone belongs to class III antiarrhythmic drugs which shares the property of all other classes of antiarrhythmic drugs. This drug is considered the most frequently used antiarrhythmic agent owing to its broad spectrum of action that make it effective in many types of arrhythmias. On one hand, it has a good clinical profile, with relatively low incidence of adverse effects if used by respecting specific prcautions and contraindications such as liver and thyroid dysfunctions. On the other hand, it

also has the potential of inducing arrhythmias, one of which is QT interval prolongation that can lead to serious polymorphic ventricular arrhythmia or torsade de pointes (TdP).[8] This type of arrhythmia is related to the mechanisms of action of amiodarone by blocking potassium channel and causes prolongation of ventricular repolarization and the refractory period, -leading to QT-interval prolongation.[9]

Beside amiodarone, some other drugs are also reported to have the potential to cause QT prolongation, such as azythromycin, haloperidol, metronidazole, cisapride, erythromyin, clozapine, etc. Adverse Drug Reaction Advisory Committee (ADRAC 2005) of Australia,[10] reported 140 cases of QTc prolongation and/or torsade de pointes. Seven of them were fatal. The most frequently implicated drugs in these reports are sotalol, cisapride, clozapine, amiodarone and erythromycin.

In the present study, we found significant frequent of QT interval prolongation in the group receiving amiodarone or other drug causing QT prolongation, either alone or in combination. It is interesting to note, that there was no further potentiation of QT interval prolongation if amiodarone was used in combination with other QT prolongation inducer drugs. This finding is different from that of Samarendra et al,[11] who reported the potentiation of QT prolongation if two groups of drugs are combined. Explanation of this different result is not clear, but it might be due to the influence of different cadiovascular background and the small sample size.

Azithromycin is a macrolide antibiotic that frequently used to treat pneumonia. It is known that patients with severe clinical conditions are prone to contract nosocomial infection or hospital associated pneumonia in which combination of antibiotics is recommended. However, in the last several years, some reports emerged on the increase of QT prolongation associated with azythromycin.[12-14] In the present study, azithromycin is the most frequent drug causing QT prolongation used by the patients, and most of them experienced QT interval prolongation. This finding is consistent with a cohort study conducted by Ray et al. on more than three hundreds patients taking azithromycin.[15] The authors found that the risk of cardiovascular death was significantly higher in patients taking azithromycin compared to those taking amoxicillin, or those taking no antibiotic, but comparable with levofloxacin.[16]

Besides concomitant drugs, we have also evaluated some other influencing factors of QT prolongation. Among these factors, hypernatremia, lung disease, and hypertension were found to have significant influence on the occurrence of QT interval prolongation. Other study by Moreno et al.,[16] (2011) also reported that hypernatremia was associated with QT interval prolongation, while gender, serum potassium level, and liver or kidney function did not show significant influence.

On theorethical point of view, hypokalemia can induce arrhythmia, since low extracellular potassium level decreases IKr,[4] an effect that is likely to contribute to QT interval prolongation. However, in this study, as well as in that of Moreno,[16] hypokalemia was not related with QT prolongation. On the contrary, some literatures reported that hypokalemia is an important risk factor of TdP development.[4,6] Explanation of this contradictory findings of hypokalemia and hypernatremia on the occurrence of QT prolongation is not well understood. The fact is sodium and potassium ions compete for access to extracellular binding sites on IKr channel and sodium is a potent blocker of this current. It can be speculated this competition might explain the occurrence of QTc prolongation in this study.

Concerning the influence of gender, Stramba-Badiale et al., (1997) reported that female gender may play determinant role in the occurrence of QT interval prolongation.[17] It is suggested that sex steroid hormones may have differential influences on ventricular repolarization, since the tendency of prolonged QT interval in female is only observed after puberty.

Concerning mortality, we observed mortality in groups receiving amiodarone or other drugs causing prolonged QT, alone or in combination. Among all mortalities, 3 was caused by sudden cardiac death, 4 due to cardiogenic shock, and others were due to pneumonia and septic shock. The role of QT interval prolongation in these mortalities could not be concluded, since

it occurred shortly after hospital admission. Thus, the severe heart attack seemed to be more possible as the cause of death.

In this study, no cases of severe arrhythmia, such as torsade des pointes, was observed. Indeed, amiodarone frequently prolonged QT interval, but the incidence of torsade de pointes was reported to be low.[6] With small sample size in our study, the probability to find the TdP was thus very low.

## CONCLUSION

From this study, we concluded that the use of amiodarone in Cipto Mangunkusumo Hospital was associated with a high incidence of QT interval prolongation, but no serious arrhythmia was observed. The use of other drugs causing QT prolongation resulted in similar incidence of QT interval prolongation. No potentiation effect was found when these two drugs were used in combination. Hypernatremia was shown as contributing factor to QTc interval prolongation.

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