Original Article

QTc Prolongation in Patients on Antipsychotic Drugs

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Summary:

Background: There is a recognized association between prolongation of the heart rate corrected QT interval (QTc) and antipsychotic drugs. QTc prolongation may increase the risk of ventricular tachyarrhythmias, especially torsade de pointes, and therefore, sudden cardiac death.

Objective: This study assess the effect of antipsychotics and prolongation of the heart rate corrected QT interval (QTC), and QTC prolongation may increase the risk of ventricular tachyarrhythmias, especially torsade de pointes and sudden cardiac death.

Methods: QT interval measured in lead II in electrocardiogram for 198 patients with psychiatric at Baghdad Teaching Hospital and AL – Rashad Teaching hospital from July to October 2001. Bazett formula was used in calculation of corrected QT. By application of the chi – square test "×2" to see the association of QTc prolongation with the cigarette smoking, age, sex, heart rate, cardiovascular disease.

Results: Abnormal QTc was defined as an interval of more than 440 ms (0.44 second) and was present in 21.7% (43 patients of 198). Benzhexol (-0.333 – 0.051 second), Fluphenazine (-0.046 – 0.671) were robust predictors of QTc lengthening, also the high antipsychotic dose and combination of antipsychotics and antidepressants were associated with higher incidence of QTc lengthening.

Conclusion: Antipsychotic drugs cause QTc lengthening in a dose – related manner. Risks are substantially higher for Benzhexol and Fluphenazine. These drugs may therefore confer an increased risk of drugs – induced arrhythmia.

Key Words: Antipsychotics, QT interval, arrhythmia.

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Introduction:

Psychotropic agents including tricyclic antidepressants (TCAs), certain antipsychotics, and selective serotonin reuptake inhibitors (SSRIs) have also been associated with QT prolongation (1). The QT interval (QTi) prolongation is a risk factor for the development of ventricular arrhythmia such as torsade de pointes (TdP) and death [2]. The normal Q.T interval is in the range of 0.35 to 0.43 sec [3,4]. The length of the QT interval decreases as heart rate increases, so, a "corrected" QT value, the QTc, is used to assess the conduction status within the heart. (5).Numerous formulas have been suggested to correct for heart rate. Bazett proposed a formula for estimating the Q.T interval corrected for heart rate. The QTc: Q-T/ √RR {by dividing the measured Q.T interval (in sec.) by the square root of the R-R interval (in sec)}. [6]QTc values > 0.44 ms are usually considered abnormally prolonged [7]. Antipsychotics share little more than their overall therapeutic effects: they differ importantly in pharmacology and widely in chemical structure,because of this, it is unlikely that all antipsychotics have the same effects on myocardial ion channels or on QT interval, or have similar pro-dysrhythmic potential. (8).The combination of antipsychotic drugs and antidepressants caused a significant QT prolongation. (9).Almost all drugs causing significant QT prolongation are known to interact with repolarizing potassium channels, particularly with the rapid component of delayed rectifier potassium currents (I_{kr}), encoded by the human Ether-a-go-go related gene (HERG) (10).

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Patients and Methods:

ParticipantsThis cross sectional descriptive study that was carried out in AL-Rashad Teaching Hospital and Baghdad Teaching Hospital. The patients were mainly from inpatient department and few of them from outpatient clinic.One hundred ninety eight psychiatric patients were enrolled in the study, there age range between 17 - 74 years (mean 39.2 years), 178 participants were from inpatient ward (90%) and 20 cases from outpatient clinic (10%), 106 (53.5%) were male and 92 (46.5%) were female.The duration of the study was between July and October 2001. The patients ages ranged between 17 – 74 years; who have psychiatric diseases on antipsychotics for more than one week for oral drugs and for more than tow months for depot drugs.

All patients who have any history of change in drug therapy within the previous one week for oral drugs and two months for depot preparations were excluded from the study. Patients with atrial fibrillation or bundle branch block were also excluded. Cases with history of alcohol drinking were also excluded. Patients with pre-existing cardiac disease were

included because they may be a group at a particular risk of drug induced repolarization abnormalities or arrhythmia.

2.2 Data collection and analysis:

Three standard leads electrocardiogram was taken at 25 mm/second with a portable electrocardiography machine.Age, gender, smoking and cardiovascular history (including arrhythmia, ischemic or valvular heart disease or hypertension) were recorded.Antipsychotic doses were converted into chlorpromazine equivalents(11). All doses were not more than 1000 mg chlorpromazine equivalents per day. Doses were classified as; 100 mg – 400 mg chlorpromazine equivalents per day, 400 – 700 mg chlorpromazine equivalent per day, and 700 – 1000 mg chlorpromazine equivalent per day.The QT interval was measured from the onset of the QRS complex to the end of the T – wave, from lead II only. When the end of the T – wave could not be identified, the patient was excluded from the analysis. QT interval was corrected for the heart rate by Bazett's formula:

$$QTc = QT \Big/ \sqrt{RR\,\text{int}\,erval}\,.$$ QTc

prolongation defined as QTc more than standard value of 440 ms (0.44 second).

2.3 Statistical analysis

All variables data were arranged and tabulated in number, percentage, mean and or standard deviation. Association between different variables were measured by using Chi – square test, Fisher>s exact test, and t-test when it is appropriate to differentiate between dependant and independent variables in their effects on the QTc interval. We used multiple regression models. The association between different variable considered to be significant when $P < 0.05$.

Results:

figure no. 1 shows distribution of cases according to QTc prolongation which shows that 21.7% (43 patients) have QTc > 0.44 second and 78.3%(155 patients)have QTc ≤ 0.44 second .Table no.1 shows the distribution of cases according to risk factors and QTc duration which shows that 5 patients were more than 60 years, one of them (20%) has QTc > 0.44 second, while 193 patients were 60 year old or younger, and 42 of them (21.8%) have QTc > 0.44 second.106 patients were male and 23 of them (21.7%) have QTc > 0.44 second 92 patients were female and 20 of them (21.7%) have QTc > 0.44. smoker patients were 138, and 27 cases of them (19.6%) have QTc > 0.44 second and 111 (80.4%) have QTc > 0.44 second. History of cardiovascular disease was positive in 10 patients, 4 of them (40%) have QTc > 0.44 second and 6 cases (60%) have QTc ≤ 0.44 second.For heart rate of more than 99 bpm, there was (24%) (20 of 83 patients) have QTc > 0.44 second and (76%) (63 of 83 patients) have QTc ≤ 0.44 second .Table no.2 shows the distribution of cases according to drugs and QTc prolongation, which shows fluphenazine and benzhexol have statistically significant QTc prolongation ,the p-value was < 0.05.While other drugs as amitryptalm, chlorpromazme, flupenthioxole, procyclidine , thiondazine , tnfluperazine ,the p-value was not significan(>0.05).

Table no. 3 shows the incidence of antipsychotics and antidepressants. In 128 patients who took antipsychotics, only 25 of them (19.5%) show QTc > 0.44 second, while 8 patients were taking antidepressants in whom only one patient (12%) show QTc > 0.44 second 62 cases were taking antipsychotics with antidepressants, in whom 17 patients (27.4%) show QTc > 0.44 second.

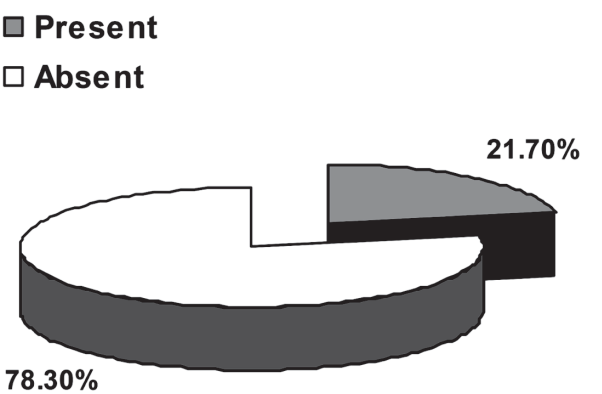

Figure (1) Pie: chart showing the result of QTC prolongation

Table (1) study the relation of different factors in comparison to QTC interval

		QTc >0.44		QTc <0.44		Total		
		No.	%	No.	%	No.	Odd ratio	P
Age	> 60	1	(20)	4	(80)	5	0.95	Ns*
	< 60	42	(21.8)	151	(78.2)	193		
Gender	Male	23	(21.7)	83	(78.3)	106	1.174	Ns
	Female	20	(21.7)	72	(78.3)	92		
Smoker	Yes	27	(19.6)	111	(80.4)	138	669	Ns
	No	16	(26.7)	44	(73.3)	60		
CVD	Yes	4	(40)	6	(60)	10	2.55	Ns
	No	39	(20.7)	149	(79.3)	188		
Heart rate	> 99	20	(24)	63	(76)	83	1.27	Ns
	< 99	23	(20)	92	(80)	115		

*NS mean not significant

Table (2): Distribution of patients according to drugs and Qtc prolongation.

Drugs	Total exposed No.	Exposed cases QTc >0.44 sec	Odd ratio	P
Amitryptaline	57	17 (29.8%)	1.880	NS*
Benzhexol	40	8(20%)	0.288	<0.05
Chlordiazepoxide	2	0	0.781	NS
Chorpromzine	17	4(23.5%)	1.120	NS
Flupenthixol	167	36(21.6%)	0.942	NS
Fluphenazine	10	4(40%)	2.547	<0.05
Haloperidol	1	0	0.782	NS
Lmipramine	8	0	0.774	NS
Procyclidine	16	3(18.8%)	0.819	NS
Thioridazine	66	13(19.7%)	0.834	NS
Trifluperazine	9	1(11.1%)	0.438	NS

*NS mean not significant

Table (3): distribution of antipsychotics and antidepressants and QTc prolongation

	QTc >0.44		QTc ≤0.44		Total	
	No.	%	No.	%	No.	P
antipsychotics	25	19.5%	103	80.5%	128	Ns*
antidepressants	1	12%	7	88%	8	Ns
Antipsychotics and antidepressants	17	27.4%	45	72.6	62	Ns

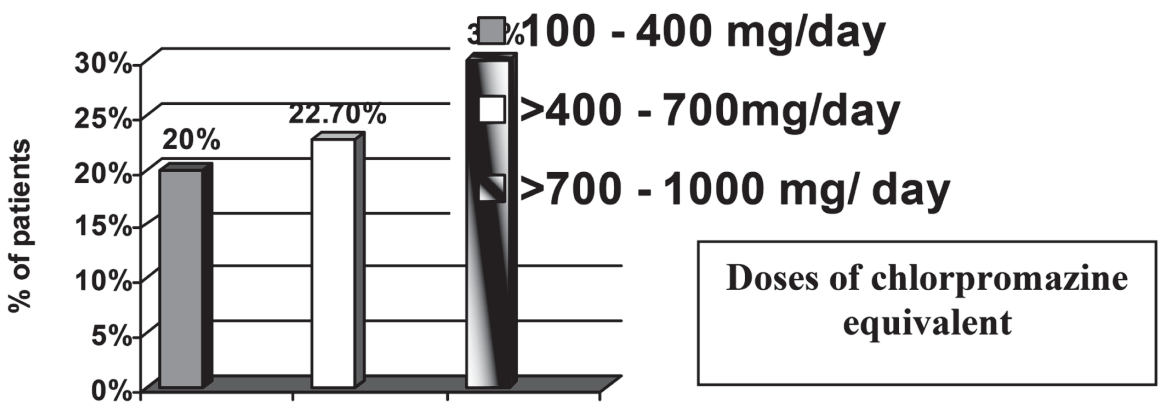

Figure (3): Relationship between QTc prolongation and antipsychotics doses (in chlorpromazine equivalents).

Discussion:

Ths study showed an association between QTc prolongation and antipsychotic drugs and with their doses.

Benzhexol and fluphenazine were robust predictors of QTc lengthening in a multiple regression model but there was no relation with the other drugs or risk factors.The limitations of the study of QTc lengthening is the variation in cut – off values for abnormality from 420 ms – 470 ms. Our prevalence of QTc lengthening in the patient group was (21.7%). This is lower than value of (23%) found with Warner et al [12] which may be explained by the lower cut – off value (420 ms) used in that study and our prevalence is higher than that of Reilly et al [13], which was (8%) which could be explained by higher cut – off value (456 ms) use in that study .

The prevalence of QTc lengthening was similar in both male and female.Tricylic antidepressants have previously been linked with QTc lengthening but the risk is usually perceived in higher dose (≥ 3.5 mg/kg/day) [14]. Our results suggest that the therapeutic doses of tricylic lengthen the QTc (29.8%). The doses are not more than 75 mg/day.Reilly et al also show tricylic lengthen the QTc in therapeutic dose with QTc > 0.456 second.The higher prevalence for risk factors in our study that correlates with QTc prolongation is cardiovascular diseases (which involve the ischemic heart disease, valvular heart disease, arrhythmias and hypertension).Other risk factors like age above 60 year old, smoking, heart rate >99 bpm have less prevalence for QTc prolongation.This was in agreement with Reilly et al(13). except for age in later study it is significantly associated with QTc prolongation.

Of the specific drug relation fluphenazine shows the most high prevalence (40%) and it's P value is less than 0.05. this results in different from other studies which show thioridazine is most frequently to QTc prolongation in therapeutic dose as in Piepho et al [15] which show QTc prolongation is (35.8%), and in overdose as in Buckley et al [16] which show significant prolonged QTc more than 450 ms with P = 0.001, while in our study thioridazine show (19.7%) prolonged QTc with P = 0.326. this may be due to the fact that most patients prescribed thioridazine in our study were given doses of 300 mg/day or less (only 8 patients given doses above 300 mg/day) ,and smale number of patients receive thioridazine in this study.

Our study also shows that antipsychotics have higher prevalence than antidepressant in QTc prolongation. This was in agreement with Fowler et al [17] in which show the ECG changes especially QT prolongation can occurs in up to 50% of patients receive antipsychotics ,while these changes occur in only (20%) of patients receive tricyclic antidepressant.Using antipsychotic and antidepressant drugs together have higher prevalence than using each group separately. This may be due to additive effects of both drugs. This was in agreement with Fasoli et al [18] but in later study they used overdose.QTc prolongation increased with higher dose of antipsychotics. This was in agreement with Reilly et al(13). but in later study they use a dose of > 1000 mg chlorpromazine equivalents per day. While in our study used 1000 mg chlorpromazine equivalents per day or less, but also showed relation between increasing the dose and increasing the QTc prolongation.Several factors limit the applicability of these results to current practice. 13 different psychotropic drugs were being used, with many patients on more than one drug. Thus our conclusions about the effects of individual drugs are limited because of small numbers in which some drugs are prescribed. Other factors which may prolong the QTc like electrolyte disturbance and hypothyroidism were unable to examine.

Conclusions:

Antipsychotic and tricyclic anti-depressant drugs cause QTC lengthening in a dose-related manner. Risks are substantially higher for fluphenazine and Benzhexol. The association between QTC lengthening and Cardiac arrhythmias and sudden death has been well documented, so these drugs may therefore confer an increased risk of drug –induced arrhythmia. QTC lengthening can occurs even with small dose and in absence of cardiovascular disease in both men and women and even in young non smoker patients. The prevalence of lengthening is higher if both Antipsychotics and antidepressants used together.

Reference:

1- Fu EY, Clemo HF, Ellenbogen KA. Acquired QT prolongation: mechanisms and implications. Cardiol Rev. 1998;6:319–324.

2- Elming H, Sonne J, Lublin HKF. The importance of the QT interval: a review of the literature. Acta Psychiatr Scand 2003: 107: 96–101.

3- Gupta VK, Aggarwal KK. Essential of Applied Electrocardiography, first Edition, New Delhi, Jaypee Brothers Medical Publishers, 1993: 56-165.

4- Goldschlager N, Goldman MJ. Electrocardiography: Essential of interpretation, Lebanon, Typopress, 1984: 196-202.

5- Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry. 2001;158:1774–1782.

6- Sagie A, Larson MG, Goldberg RJ, et al. An Improved Method for Adjusting the QT Interval for the Heart Rate. American Journal cardiology 1992; 70: 797.

7- De Luna B. Textbook of Clinical Electrocardiography, Netherlands, Martinus NiJhoff Publishers, 1987: 45-395.

8- Taylor DM. Antipsychotics and QT prolongation. Acta Psychiatr Scand 2003: 107: 85–95.
9- Michela S ,Alessandro V , Paolo B , et al. prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy Annals of General Psychiatry 2005, 4:1.
10- Tie H, Walker BD, Valenzuela SM, Breit SN, Campbell TJ: The Heart of Psychotropic drug therapy. Lancet 2000, 355:1825.
11- Jann MW, Ereshefsky L, Saklad RS. Clinical Pharmacokinetics of the Depot Antipsychotic. Clinical Pharmacokinetics, 1985; 10:315-333.
12- Warner JP, Barner TR, Henry J A.Electrographic in patients receiving neuroleptic medication . Acta Psychiatry Scand 1996;93:311-313.
13- Reilly JG, Ayis SA, Ferrierin ,et al .QTC interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000;355:1048-1052.
14- Giardinia EG ,Bigger JT ,Glassman AH,et al. The electrographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 1979;60:1045-1052.
15- Piepho RW. Cardiovascular effects of antipsychotics used in Bipolar Illness .J. Clin Psychiatriy 2002 ;63:20-23.
16- Buckley ND,Whyte IM,Dawson AH. Cardio toxicity more common in thioridazine overdose than with other
17- Fowler NO,Mccall D,Chou TH,et al. Electrographic changes and cardic arrhythmias in patients receiving psychotroic drugs ,The American Journal of Cardiology 1976;37:223-230.
18- Fasoli R,Glauser F. Cardiac arrhythmias and ECG abnormalities in tricyclic antidepressants over dose .Clin. Toxical 1981;18:155.1.