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Medication-Induced Variations on Electrocardiographic Patterns: A Contrast between Atypical Antipsychotics

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Abstract

Introduction: Prolongation of the Q-Tc interval is commonly accepted as a surrogate marker for the ability of a drug to cause torsade de pointes (TdP). In the present study, safety of olanzapine vs. risperidone was compared among a cluster of schizophrenic patients, to see the frequency of the electrocardiographic alterations that can be induced by those atypical antipsychotics.

Method: Two hundred and sixty-eight female schizophrenic inpatients entered in one of the two parallel groups, to participate in an open study for random assignment to olanzapine (n=148) or risperidone (n=120). Standard 12-lead surface ECG was taken from each one of them at baseline, before initiation of treatment, and then at the end of management, just before discharge. The parameters that had been assessed included: heart rate (HR), P-R interval, QRS interval, Q-T interval (corrected = Q-Tc), Ventricular Activation Time (VAT), ST segment, T wave, Axis of QRS and finally inter-ventricular conduction process.

Results: 37.83% of the cases in the olanzapine group and 30% of them in the risperidone cluster showed some Q-Tc changes. 13.51% and 24.32% of the patients in the olanzapine group showed prolongation and shortening of the Q-Tc, respectively. But, the altered cases in the risperidone group showed only prolongation of Q-Tc. Comparison of means showed a significant increment in Q-Tc by risperidone ($p = 0.02$). Also, Comparison of proportions, showed significantly more cases with shortening of QT-c against cases with its prolongation in the olanzapine group ($p =0.01$). No significant alterations with respect to other variables were evident. Post-hoc power analysis demonstrated an acceptable power of 0.88 regarding this trial.

Conclusion: Both of olanzapine and risperidone had comparable potentiality for induction of Q-Tc changes, whilst production of further miscellaneous alterations in ECG was more observable by olanzapine, in comparison with the other one. Also shortening of Q-Tc was specific to olanzapine. In addition, the risk of serious cardiac events does not seem to be independent from the extent of Q-Tc alteration.

Keywords: Electrocardiography; Second generation antipsychotics; Olanzapine; Risperidone; Q-Tc

Introduction

The risk of sudden cardiac death for individuals receiving antipsychotic drugs is about 2.4 times greater than that for nonusers [1]. Prolongation of the Q-Tc interval is commonly accepted as a surrogate marker for the ability of a drug to cause torsade de pointes (TdP). Although an absolute Q-Tc interval of >500 msec or an increase of 60 msec from baseline is regarded as indicating an increased risk of TdP, but TdP can occur as well with lower Q-Tc values or changes[1,2]. Generally, the normal Q-Tc should not exceed 0.42s in men and 0.43s in women [3]. According to Reilly, 8% of the psychotropic drug users had Q-Tc interval measurements two standard deviations greater than the mean for the normal comparison subjects, which rose to 15% among subjects taking both tricyclic antidepressants and antipsychotic drugs (especially thioridazine) [4]. Also, an increased risk of mortality (1.6 to 1.7 times greater), possibly due to heart failure or sudden death, has been reported with the use of olanzapine in the treatment of old patients with dementia, and so it has not been approved by the FDA for use in the treatment of such patients [5]. In the present study, safety of olanzapine vs. risperidone was compared among a cluster of schizophrenic patients, to see the frequency of electrocardiographic changes that can be induced by those atypical antipsychotics.

Methods

Two hundred and sixty eight female inpatients with diagnosis of schizophrenia, according to the criteria of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision, were entered in either of the two parallel groups, to participate in an open study for random assignment to olanzapine (n=148, 5–25 mg/day) or risperidone (n=120, 4–8 mg/day). After complete description of the study to the subjects, written Informed consent was obtained from either the participant or a legal guardian or representative. Also, the patients were free to stop the medication if they wished. Any patient with any diagnosed medical (like sever renal or liver disease) or cardiovascular problem (like tachycardia, bradycardia, interventricular conduction defect, ischemic heart disease, myocardial or pericardial disease, congestive heart failure), electrolyte disturbances (hypocalcaemia , hypercalcemia, hypomagnesaemia, hypokalemia, hyperkalemia), cerebral or subarachnoid injury, and also patients who were utilizing other concomitant drugs (like digitals that shortens Q-Tc or quinidine, procainamide and amiodarone that increase that , or utilization of mood stabilizers, antidepressants or depot antipsychotics) or cases more than 40 years old had been excluded from the trial. Thus, the aim of the study was to determine electrocardiographic changes in healthy schizophrenic patients**.** After a minimum 7-day washout period, both of theses drugs were prescribed according to practice guidelines and standard-titration protocols [6] and in accordance to the following regimen: 1 mg/day of risperidone or 5 mg/day of olanzapine at baseline up to 2 mg/day of risperidone and 10 mg/day olanzapine at the end of the first week. Weekly interval increments of 2 mg for risperidone and 5 mg for olanzapine, individually and according to clinical situation, up to maximum of 8 mg and 25 mg for risperidone and olanzapine, respectively at week 5. The 5th week dosage remained constant up to the end of the study. Standard 12-lead surface ECG was taken from each patient at baseline, before initiation of the antipsychotic, and than again at the end of the treatment, just before discharge (in the sunrise, before initiation of daily prescription). No other psychotropic drug was permitted during the assessment. The parameters that had been assessed included: heart rate (HR), P-R interval, QRS interval, Q-T interval (corrected = Q-Tc), Ventricular Activation Time (VAT), ST segment, T wave, Axis of QRS and finally inter-ventricular conduction process. Although it is a standard practice to measure the QT interval from the beginning of the QRS complex to the end of the T wave, but the actual methods of measurement have not been standardized yet and in addition dissimilar opinions exist regarding the most useful method for correction of

Q-T interval for heart rate (such as *Bazett formula*, *Fridericia cube-root correction* or *Framingham linear regression equation*) [2]. In this experiment, measurement of Q-T interval was based on *'expert opinion guidelines for measuring the QT interval'* [2]. Also, calculation of heart rate was based on the *'modified table of Ashman R & Hull E'*, and correction of the observed Q-T interval, based on R-R interval, was done according to the '*Kissin's nomogram* ' for rate correction of Q-T interval [6]. Moreover, since the purpose of the current assessment involved detection of various alterations of ECG, caused by the abovementioned drugs, so no definite criterion was set for a clinically meaningful alteration in Q-Tc or other related parameters.

Statistical Analysis

Patients were compared on baseline characteristics by 'chi-square tests' for categorical variables and 't tests' for continues variables. Also, the results were analyzed by 't test 'or 'compression of two proportions' for intra-group and between-group analysis. Statistical significance was defined as a 2-sided p value < or = to 0.05. MedCalc, version 9.4.1.0, was used as statistical software tool for analysis.

Results

Groups were initially comparable and demographic and diagnostic variables were analogous. (Table1) 37.83% (n=56) of the cases in the olanzapine group and 30% (n=36) of them in the risperidone cluster showed some Q-Tc changes (comparing baseline to post-treatment stage). In addition, 13.51% (n=20) and 24.32% (n=36) of the patients in the olanzapine group showed prolongation (0.01-0.04Sec, mean=0.02+/-0.01Sec) and shortening (0.01-0.04Sec, mean=0.02+/-0.01Sec) of the Q-Tc interval, respectively. This reduction in Q-Tc was equivalent to 0.04 Sec in at least 5.40% (n=8) of the patients. But, the altered cases in the risperidone group showed only prolongation of Q-Tc (0.01-0.02Sec, mean=0.016+/-0.005Sec). Comparison of proportions, between olanzapione and risperidone, regarding total number of the altered cases in their groups, was non-significant (z = 1.34, p =0.17, 95%C I = -0.03, 0.19). Besides, in the olanzapine group, comparison of means between baseline Q-Tc vs. its post-treatment measurement, and also post-treatment Q-Tc in the olanzapine group against comparable variable in the risperidone group were non-significant. But comparison of means, between baseline Q-Tc of risperidone group versus its post-treatment measurement showed a significant increment (p = 0.02) (Table 2). In addition, comparison of proportions in the olanzapine group showed that the quantity of the cases with shortening of Q-Tc was significantly more than the number of the patients with Q-Tc prolongation (z = -2.37, p =0.01, 95% CI = -0.19, -0.01). Moreover, 5.40% (n=8) of the patients in the olanzapine group showed alteration of P-R interval. Four of them showed prolongation (0.02 Sec) and the other ones shortening of that (0.02 Sec). But at the end, such an alteration was non-significant, in comparison with baseline, in the related group (p = 0.15) (Table 2). In the later cluster two of them had synchronized increment of Q-Tc and P-R interval. It is mentionable that there was no P-R alteration in the risperidone group. Intra-group analysis did not show any significant difference in HR, VAT and QRS complex, between baseline and closing stage of the treatment, in both of the aforesaid groups. (Table2) Moreover, no shifting in the S-T segment (depression or elevation) or T wave's alteration was evident among those cases. In the olanzapine group, two patients showed left anterior hemi-block, in accompany with mild shortening of Q-Tc (0.01Sec). No serious adverse effect, like torsade de pointes, Brugada syndrome, ventricular tachyarrhythmia, Ventricular fibrillation and sudden death occurred throughout this experiment. The mean modal dose of Olanzapine during the present assessment was 19.49±5.51 mg/day. The most common dosages of olanzapine were 20 mg /day (n=98, 66.21%), 25mg/day (n=26, 17.56%) and 15 mg/day (n=24, 16.21%). The mean modal dose of risperidone throughout the experiment was 5.14±2.86. Its most common doses were 6mg/day (n=58, 48.33%), 8 mg/day (n=48, 40%) and 4 mg/day (n=16, 13.33%). Also during the study, 26.66% (N=32) of the cases in the risperidone group and 9.45 % (N=14) of them in the Olanzapine group showed extra-pyramidal side effects. Increase in weight, was significantly greater in the patients treated with olanzapine (n=34, 22.97%) than in those treated with risperidone (n=10, 8.33%). The mean weight gain by olanzapine and risperidone was about 2.2± 0.91 kg and 0.6±0.75kg, respectively. Post-hoc power analysis demonstrated an acceptable power of 0.88 [n1=148, n2=120, alpha = 0.05, critical t (266) =1.65] as regards this trial.

Variables	Olanzapine (n=148)	Risperidone (n=120)	X2	t	df	P	95%CI
gender, female	100%	100%					
age, mean of years	25.63±6.01	23.92±5.87		1.747	266	0.082	-3.64 to 0.224
Married cases	118	94	0.279		1	0.7798	-0.083to0.111
duration of treatment prior to discharge, mean of days	24.54±22	20.7±7.25		1.394	266	0.165	-9.28 6 to 1.606
baseline heart rate	86.91±27.5	92±21.5		1.244	266	0.215	-2.99 to 13.17
baseline P-R interval	0.13±0.06	0.14±0.05		1.094	266	0.275	-0.008 to 0.028
baseline QTc	0.41±0.08	0.40±0.04		1.890	266	0.174	-0.041 to 0.001
baseline QRS complex	0.082±0.02	0.079±0.02		1.822	266	0.0705	-0.0125 to 0.0005
baseline VAT	0.030±0.01	0.028±0.007		1.394	266	0.165	-0.0048 to 0.0008

Table 1: Baseline Demographic & Electrocardiographic Characteristics of Participants.

Drug\Variable	Mean or number at baseline	Mean or number at ending	t	DF	P	CI
olanzapine-HR	86.91±27.5	84.45±22.5	0.84	294	0.40	-3.29, 8.21
Risperidone-HR	92±21.5	89±21	1.09	238	0.27	-2.40, 8.40
olanzapine-P-R interval	0.13±0.06	0.14±.06	-1.4	294	0.15	-0.02, 0.00
Risperidone-P-R interval	0.14±0.05	0.14±0.05			>0.05	
olanzapine-QRS	0.082±0.02	0.082±0.02			>0.05	
Risperidone-QRS	0.079±0.02	0.079±0.02			>0.05	
olanzapine-VAT	0.030±0.01	0.030±0.01			>0.05	
Risperidone-VAT	0.028±0.007	0.028±0.007			>0.05	
olanzapine-QTc	0.41±0.08	0.41±0.07	0.00	294	1.00	-0.02, 0.02
Risperidone-QTc	0.40±0.04	0.41±0.025	-2.32	238	0.02	-0.02, -0.00
olanzapine-Normal axis (Vector)	100%(n=148)	97.29%(n=144)			0.440	
Risperidone- Normal axis(Vector)	100%(n=120)	100%(n=120)			>0.05	
olanzapine-normal interventricular conduction	100%(n=148)	97.29%(n=144)			0.440	
Risperidone- normal interventricular conduction	100%(n=120)	100%(n=120)			>0.05	
olanzapine-upright T wave	100%(n=148)	100%(n=148)			>0.05	
Risperidone- upright T wave	100%(n=120)	100%(n=120)			>0.05	

Table 2: Intra-group analysis of various variables, between starting point and final stage of evaluation.

Discussion

Purpose of the present evaluation consisted of a comparison between olanzapine and risperidone, regarding their effects on ECG of the schizophrenic patients. According to the findings of this study, generally there were more tendencies in the olanzapine group to show different alterations in the post-treatment ECG of the patients. These alterations included mostly Q-Tc shortening or prolongation, and also left anterior hemi-block and P-R interval shortening or prolongation. Moreover, in the olanzapine group, there were significantly more cases with Q-Tc shortening, in comparison with its prolongation. But conversely, significant increment of mean Q-Tc had been induced only by risperidone in the present assessment, while numerically there was no significant difference between those two groups regarding Q-Tc changes. In spite of all of the aforesaid alterations, fortunately in the present assessment, there was no serious cardiac event or increase of Q-Tc in any sample to more than 0.06 second, in comparison with the baseline, or really to more than 0. 5second throughout the appraisal. So, the risk of TdP does not seem to be independent from the extent of QTc changes, whether its prolongation or shortening. Therefore, disregard to the issue of fatality, while our results were more or less in harmony with the findings of Ravin DS, et al. [7] and Yerrabolu M, et al. [8] as regards the effect of risperidone on QT interval , it is against Czekalla J, et al. [9] who stated that "risperidone can be used safely in elderly patients, who are often taking several medications, without risk of increased Q-T dispersion" . Also, with respect to olanzapine , while our results were not in agreement with Janion M, et al. [10] who stated that "olanzapine is relatively safe and does not contribute significantly to a Q-Tc prolongation that could result in potentially fatal ventricular arrhythmias" [10], it is relatively in prolongation and ventricular fibrillation. (11) accord with Mehul Desai, et al. regarding potentiality of olanzapine for induction of Q-T interval In spite of absence of cardiac events in the present assessment, but anyhow it must be bearded in mind that that TdP may occur as well with lower Q-Tc values or changes, and Q-Tc change of as little as 10 msec may indicate a 'signal' that a drug may perhaps carry an arrhythmic liability, and essentially there is no established threshold below which prolongation of the Q-T interval is considered free of pro-arrhythmic danger [1,2]. On the other hand, shortening of Q-Tc by olanzapine, had not been expressed previously in the literature. In essence, little information is known about the issue of drug-induced QT/QTc shortening [12]. As with QT/QTc prolongation, there are genetic syndromes and pharmaceutical agents which may cause shortening of QT/QTc. Although the potential safety issue of QT/QTc shortening and its suitability as a biomarker of drug-induced cardiac arrhythmias are indistinguishable, however, the type of arrhythmia associated with prolongation and shortening seems to differ. Prolongation is associated with TdP, whereas, shortening of QT/QTc is proposed to be associated mainly with ventricular fibrillation (VF). Current clinical epidemiological evidence suggests that excessive shortening of QT/QTc may facilitate induction of VF [12]. Acquired QT/QTc shortening has been reported to be caused by hypercalcaemia, hyperkalemia, hyperthermia and myocardial ischemia; problems that had been excluded from the present assessment by initial exam. But nevertheless, since the sample included only low risk, young and healthy female schizophrenic patients, then limitations against its generalization are understandable. Also the normal variation in cardiac parameters within individuals must not be ignored, because even Q-Tc can vary considerably in 2 ECGs gathered minutes apart**.** Short duration of study (limited to the period of acute treatment), gender-based sampling, lack of placebo arm, which may have significant impact on the assay sensitivity of the study, and a bit small sample size, were among the prominent weaknesses of this trial. Further analogous trials in future can improve our knowledge with respect to this vital subject.

Conclusion

Both of olanzapine and risperidone had comparable potentiality for induction of Q-Tc changes, whilst production of further miscellaneous alterations in ECG was more observable by olanzapine, in comparison with the other one. Also shortening of Q-Tc was specific to olanzapine. In addition, the risk of serious cardiac events does not seem to be independent from the extent of Q-Tc alteration.

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