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Research Article

Electrophysiology of The Heart: A Contrast Between Second Generation Antipsychotics

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Abstract

Introduction: Extension of the Q-Tc interval is usually accepted as a proxy indicator for the ability of a medication to cause 'Torsade de Pointes' (TdP). In the current study, safety of olanzapine against risperidone was compared amongst a cluster of schizophrenic patients, to see the incidence of the electrocardiographic variations that can be induced by those newer antipsychotics.

Method: Two hundred and sixty-eight female schizophrenic patients had been divided into one of the parallel groups, to take part in an open-label investigation for random assignment to olanzapine or risperidone. Typical twelve-lead surface EKG had been taken from each one of patients at starting point, before initiation of management, and at the end of treatment, before discharge from hospital. The parameters that had been measured involved: '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 pattern.

Results: 37.83% of cases in the olanzapine group and 30% of them in the risperidone group displayed some Q-Tc variations. 13.51% and 24.32% of the patients in the olanzapine group exhibited extension and shortening of the Q-Tc, separately. But, the changed cases in the risperidone group exposed merely continuation of Q-Tc. 'Comparison of means' revealed a substantial increase in Q-Tc by risperidone ($p < 0.02$). Similarly, 'Comparison of proportions', presented meaningfully more cases with shortening of QT-c in comparison with cases with its prolongation in the olanzapine group ($p<0.01$). No important modifications with regard to other parameters were obvious. 'Post-hoc' power analysis revealed an acceptable power of 0.88 as regards this assessment.

Conclusion: Both of olanzapine and risperidone had analogous possibility for generation of Q-Tc alterations, whereas production of more variations in ECG was more discernible by olanzapine, in comparison with risperidone. Moreover, shortening of Q-Tc was limited to olanzapine.

Keywords: Electrocardiography; Second Generation Antipsychotics; Olanzapine; Risperidone; Q-Tc

Introduction

Death from sudden cardiac arrest (SCA) claims over 300,000 US lives annually – more than deaths from lung, breast and colon cancers combined [1]. Causes of SCA can range from common heart diseases such as coronary artery disease and cardiomyopathies to rare ion-channel disorders such as long-QT syndrome or the Brugada syndrome [1]. Treatment with some psychiatric medications may also increase the risk of SCA. Tricyclic antidepressant medications (TCAs) act like Type I antiarrhythmic medications in myocardial tissue. They cause sodium channel blockade and can prolong ventricular conduction. As a result, these medications may decrease the frequency of premature ventricular contractions and prolonged QT interval with resultant increase in the risk of torsade de pointes [1]. As such, caution should be exercised in patients who are already prone to a prolonged QT interval, such as those patients with a congenital prolonged QT syndrome or those patients receiving other medications that may prolong the QT interval.

TCAs may also contribute to an increase in heart rate due to inhibited synaptic norepinephrine reuptake and anticholinergic effects. These risks are theoretically present with bupropion and trazodone, though there are studies that establish the safety of their use in a cardiac population and they are commonly used in clinical practice [2]. Though many of these effects are sub-clinical, newer antidepressants, like Selective Serotonin Reuptake Inhibitors (SSRIs), are equally effective at treating depression and anxiety and do not carry the same risk of cardiac conduction abnormalities as the TCAs [2]. Neuroleptic agents can also increase the QT interval. First generation antipsychotic medications, like haloperidol and chlorpromazine, and second-generation antipsychotic medications,

like risperidone and olanzapine, have all been shown to increase the duration of the QT interval on EKG, and as such, carry some risk of development of torsade de pointes. This risk tends to be dose dependent. Of the second-generation antipsychotic medications, aripiprazole and olanzapine seem to carry the lowest risk, though head to head trials designed to clarify the relative magnitude of risk have not been conducted [3].

The effect of mood stabilizing medications on the QT interval has not been as well studied. One small study found that QT duration did directly correlate with lithium serum concentration in psychiatric inpatients carrying a bipolar disorder or schizophrenia diagnosis. Of the 39 participants, no patients had a QTc greater than 480ms [3]. So far, no torsade de pointes associated with treatment with lithium has been reported [3]. Another small study compared the effects on the QT interval of lithium treatment against combined valproic acid plus lithium treatment and found that valproic acid plus lithium group had a less pronounced effect on the QT interval than lithium, though both sets of patients had QT intervals that exceeded those from healthy control participants [4]. Methylphenidate has also been associated with sudden cardiac arrest in children [5]. This retrospective case-control study showed a six- to seven-fold increase in the odds of sudden arrest while excluding decedents with conditions known to contribute to sudden death, such as Wolff-Parkinson-White syndrome and diagnosed prolonged QT interval [5]. In the present study, olanzapine and risperidone had been compared with each other, in a group of schizophrenic patients, to see the incidence of electrocardiographic changes that may be caused by them.

Method

Two hundreds 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 into one of the parallel groups, to take part in an open-label investigation for random assignment to olanzapine (n=148, 5–25mg/day) or risperidone (n=120, 4–8mg/day). After complete explanation of the assessment to the subjects, printed informed agreement was gotten from either the participant or a legal caretaker. Besides, the patients were free to stop the medicines if they desired. Any patient with any identified medical or cardiovascular problem (like congestive heart failure, interventricular conduction defect, ischemic heart disease, myocardial or pericardial disease, tachycardia, bradycardia), electrolyte disturbances (hypercalcemia, hypocalcemia , hypokalemia, hyperkalemia hypomagnesaemia), cerebral or subarachnoid injury, and also patients using other concomitant drugs (like quinidine, procainamide and amiodarone, which increases Q-Tc or digitals, which shortens it, or mood stabilizers, antidepressants or depot antipsychotics) or cases more than 40 years old had been omitted from the appraisal. Accordingly, the purpose of study was to discern electrocardiographic alterations in fit schizophrenic patients. After at least 7-day washout period, olanzapine and risperidone were prescribed in line with practice guidelines and standard-titration protocols [6] and in accord to the this regimen: 1mg/day of risperidone or 5mg/day of olanzapine at starting point up to 2mg/day of risperidone and 10mg/day olanzapine at the end of the 1st week. Weekly interval increases of 2mg for risperidone and 5mg for olanzapine, separately and in keeping with clinical condition, up to maximum of 8mg and 25mg for risperidone and olanzapine, respectively, at week 5. The 5th week dose remained unbroken up to the end of the assessment.

Standard 12-lead surface EKG was taken from all patients at starting point, before initiation of antipsychotic, and at the end of the treatment, just before discharge from the hospital (in the sunrise, before beginning of daily prescription). No other psychotropic medicine was allowable in the course of evaluation. The parameters that had been evaluated involved: Q-T interval (corrected = Q-Tc), Axis of QRS, P-R interval, QRS interval, heart rate (HR), Ventricular Activation Time (VAT), T wave, ST segment, and finally inter-ventricular conduction pattern. Measurement of Q-T interval was based on 'expert opinion guidelines for measuring the QT interval'. [2] Likewise, control of HR was grounded on 'modified table of Ashman R & Hull E', and correction of observed Q-T interval, based on R-R interval, was done according to the 'Kissin's nomogram for rate correction of Q-T interval [7].

Statistical Analysis

Patients were compared on baseline characteristics by 'chi-square tests' for categorical variables, and 't tests' for continues parameters. Besides, the outcomes were analyzed by 't tests' or 'compression of 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 present analysis.

Results

Table 1: Baseline characteristics of participants.

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		1.89	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

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 olanzapine 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.

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

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	0.4	-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	294	1	-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)			0.44	
Risperidone- Normal axis (Vector)	100%(n=120)	100%(n=120)			>0.05	
Olanzapine-normal interventricular conduction	100%(n=148)	97.29%(n=144)			0.44	
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	

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). Furthermore, 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 starting point, in the associated group (p < 0.15) (Table 2). In the later cluster two of

them had synchronized increase of Q-Tc and P-R interval. Besides, there was no P-R alteration in the risperidone group. Intra-group analysis did not display any important difference in HR, VAT and QRS complex, between starting point and final stage of the management, in both groups (Table 2). Additionally, no shifting in the S-T segment (depression or elevation) or T wave's alteration was manifest amid those samples. In the olanzapine group, two patients exposed left anterior hemi-block, in accompany with slight shortening of Q-Tc (0.01Sec). No serious adverse effect, like Torsade de Pointes, Brugada syndrome, ventricular tachyarrhythmia, ventricular fibrillation and sudden death had happened all through this research.

The mean modal dose of Olanzapine during the evaluation 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 revealed extra-pyramidal adverse effects. Increase in weight, was meaningfully greater by olanzapine (22.97%) than in those who received risperidone (8.33%). The mean weight gain by olanzapine and risperidone was around 2.2± 0.91 kg and 0.6±0.75kg, respectively. 'Post-hoc' power analysis revealed a satisfactory power of 0.88 in respect of present appraisal.

Discussion

While purpose of the present evaluation consisted a comparison between olanzapine and risperidone regarding their effects on ECG of the schizophrenic patients, according to the findings, generally there were more trends in the olanzapine group to display different changes in the final ECG. These variations comprised Q-Tc shortening or prolongation, plus left anterior hemi-block and P-R interval shortening or prolongation. Likewise, in the olanzapine group, there were meaningfully more cases with Q-Tc shortening, in comparison with its prolongation. On the other hand, in the present assessment important increment of mean Q-Tc had been prompted merely by risperidone. In spite of all abovementioned variations, luckily in the present assessment, no serious cardiac event or increase of Q-Tc to more than 0.06 second was evident. Hence, while our results were more or less in harmony with the conclusions of Ravin et al. [7] and Yerrabolu et al. [8] regarding the effect of risperidone on QT interval , it is against Czekalla et al. [9] who stated that "risperidone can be used securely in elderly patients, who are often taking several prescriptions, without danger of increased Q-T dispersion". Moreover, with regard to olanzapine , while our outcomes were not in agreement with Janion et al. , who stated that "olanzapine is comparatively safe and does not contribute meaningfully to a Q-Tc prolongation that could result in potentially fatal ventricular arrhythmias" [10], it is relatively in harmony with Desai et al., regarding potentiality of olanzapine for induction of Q-T interval prolongation and ventricular fibrillation [11]. Despite absence of cardiac events in the current appraisal, but anyway it should be considered that TdP may happen as well with lower Q-Tc values or variations, and Q-Tc change of as little as 10msec may designate a 'signal' that a medication may perhaps carry an arrhythmic danger, and principally there is no well-known threshold below which prolongation of the Q-T interval is considered free of pro-arrhythmic risk.

[1,2] Alternatively, 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 aptness as a biomarker of drug-induced cardiac arrhythmias are vague, however, the type of arrhythmia associated with prolongation and shortening seems to differ. Prolongation is associated with TdP, whereas, shortening of QT/QTc is suggested to be linked primarily 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 instigated by hyperkalemia, hypercalcaemia, hyperthermia and myocardial ischemia; problems that had been excluded from the present assessment by initial exam. Anyhow, since in the present evaluation the sample included only young and healthy female schizophrenic patients, so limitations against generalization of the outcomes are comprehensible. Also, the normal variation in cardiac parameters within individuals should not be overlooked, because even Q-Tc can vary considerably in 2 ECGs gathered minutes apart. Short duration of study, which was limited to the period of acute management, 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 noticeable weaknesses of the present assessment. No doubt, more similar investigations in future can improve our knowledge with respect to this vital subject

Conclusion

Both of olanzapine and risperidone had analogous possibility for generation of Q-Tc alterations, whereas production of more variations in ECG was more discernible by olanzapine, in comparison with risperidone.Moreover, shortening of Q-Tc was limited to olanzapine.

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