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Comparing of the effect perphenazineand risperidone drug on electrocardiographic

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ABSTRACT

Sudden deaths due to heart disease have been sharply increased in psychiatric sections, and on the other hand, antipsychotics have been largely administrated in the treatment of psychiatric disorders, so, this study was performed to investigate Comparing of the effect perphenazine and risperidone drug on electrocardiographicin patients with schizophrenia.The current researchwas an analytical-descriptive study on 240 patients with schizophrenia disorders referred to Farabi Hospital in Kermanshah in the years 2015-2016. Patients were randomly divided into two groups, each with 120 persons. One group received 24 mg of perphenazine daily, and the other group received 6 mg risperidone, daily. To collect data, demographic and electrocardiographs were used. Data were analyzed using independent t-test, Mann-Whitney U test and Friedman test. There was no significant difference in PR between two groups. 4 cases had long PR (1.7 percent) and 3 cases had reverse T (1.2 percent). The Q-T was significantly increased in two groups, but QTc was significantly increased only in risperidone consumers. Only one abnormal QTc (480 ms) was seen amongrisperidoneconsumers. After 4 weeks, the mean QTc was 323 milliseconds in perphenazine consumers, and 330 milliseconds in risperidone consumers. After 8 weeks, the mean QTc was 324 milliseconds in perphenazine consumers, and 332 milliseconds in risperidone consumers. The increases was significant in women, but were within normal limits. Due to the significant increase in QTc in risperidone consumers, studies with larger sample sizes and longer distances ECGs may show electrocardiogram changes.

***Key Words:** Risperidone, Perphenazine, Schizophrenia, Electrocardiogram.*

INTRODUCTION

Its more than 5 decades that antipsychotic are used for the treatment of bipolar disorder, delirium, delusional disorder, psychotic depression, schizophrenia and substance-related psychosis [1]. The first antipsychotics were used for the treatment of schizophrenia psychosis and bipolar disorder in 1950. Antipsychotics are classified into two categories: Typical antipsychotics block D2 receptors and atypical ones block D2 and 5HT2A receptors in the central nervous system. Both groups reduce psychosis positive symptoms, such as hallucinations, delusions and disorganized thoughts. The first generation or typical antipsychotic, have less affinity toward 5HT2A than dopamine D2 receptors, and are more likely to cause extrapyramidal side effects. Second-generation or atypical antipsychotic, block 5HT2A and D2 receptors with high affinity. This causes less extrapyramidal side effects. In the past decade the use of antipsychotic has significantly increased [2-4]. Recent studies have shown that in patients with schizophrenia and other mental disorders, the risk of dying from cardiovascular disease is 2-3 fold greater, and this may be due to the use of first and second generation of antipsychotic drugs, wrong lifestyle, and smoking, lack of exercise and drug abuse [2]. Risk factors for cardiovascular disease, along with the use of atypical antipsychotics include oldness, impaired autonomic system, history of cardiovascular disease, being female and electrolyte imbalance (hypokalemia, and hypomagnesium), increased serum levels of antipsychotic drugs, genetic characteristics and psychiatric disease [1,5,6]. With the arrival of second-generation antipsychotics in 1990, cardiovascular mortality was increased. In a study by Lang et al (2012), it was reported that patients with untreated psychosis have no higher risk of heart disorders than the general population, but by the use of antipsychotics, this risk was increased rapidly. Because of the increased cardiovascular mortality induced by antipsychotics, related cardiovascular risk factors are become the focus of interest [7]. Increased activity of the sympathetic system by antipsychotic drugs, increases the risk of QT prolongation and cardiac arrhythmia [2]. ECG changes induced by antipsychotic drugs include long QT, wide QRS, ST segment depression and T-wave abnormalities and large U wave which together indicate abnormal depolarization [8-10]. Most antipsychotic drugs also lower blood pressure when standing up. Increase in heart rate was observed in the use of antipsychotics. Epidemiological studies have shown that the use of antipsychotics increase the risk of sudden cardiac death, and somewhat prolong the QT interval. Long QT increases the likelihood of progression to ventricular arrhythmias such as torsad depoint, especially in susceptible individuals [11-15]. Research has shown that in the general population, the average QT interval is longer in women than men, and this could be related to race and age. Specific factors that influence the QT interval include genetic factors on chromosomes 7 and 11 and age. With every 10 years of age, QT interval is increased about 10ms, and this increase is more in white women [16]. The use of anti-psychotics in psychiatric disorders such as psychosis, bipolar disorder and depression has been increased, and in many psychiatric diseases, related cardiovascular complications must be more studied. Thus, according to an increasing incidence of sudden deaths in psychiatric wards, this study examines the relationship between both types of antipsychotics and electrocardiographic changes.

MATERIALS AND METHODS

The current research is an analytical-descriptive study. The study population included all schizophrenia patients in Farabi Hospital Kermanshah in 2015 – 2016, among which 240 patients were placed in two groups randomly, each with 120 patients. Inclusion criteria were: all patients with schizophrenia that were diagnosed according to DSM IV-TR criteria by a psychiatrist, lack of hospitalization and the use of antipsychotics histories. Exclusion criteria were: patients with hypothyroidism, heart disease, such as arrhythmias, ischemic diseases and heart failure, medical conditions such as severe liver disease and kidney disease, drugs that change the QT (e.g. TCA, quinidine, procainamide, and amiodarone), taking other psychiatric drugs, electrolyte disturbances such as hypokalemia, hyperkalemia, hypocalcaemia and hypomagnesaemia, smoking and drug abuse.

In this study, patients were placed in two groups, risperidone and antipsychotic consumers, based on the last digit of national number. The first group received 24 mg of perphenazine (typical antipsychotic) and the second group received 6 mg risperidone

(atypical antipsychotic). On admission, ECG was recorded from all patients at a speed of 25 mm/s and then, after 4 weeks and 8 weeks, electrocardiogram was recorded again. All patients were assessed with the same device and QT intervals and other electrocardiogram changes were evaluated and Qc (corrected) interval was calculated based on the formula QTc = QT + 1.75 (HR-60). The ECG was evaluated by a cardiologist. In terms of age and gender, groups were trying to be homogeneous.

For statistical analysis of the data, the mean and standard deviation of all the variables were examined. Chi-square, Mann-Whitney U and Friedman tests were used for analysis. The statistical significance level at all of the tests was considered to be 0.05.

FINDINGS

Table 1. The general characteristics of the study population

Variable	**Levels**	**Drug type(%) n**		**Total**	**Chi square**	**DF**	**P Value(**
		Risperidone	**Perphenazine**				
Gender	Female	55 (45.8%)	49 (40.8 %)	104 (43.3%)	0.611	1	0.515
	Male	65 (54.2%)	71(59.2%)	136 (56.7%)			
Marital status	Single	63 (52.5%)	45 (45 %)	117(48.8%)	3.006	3	0.391
	Married	47 (39.2%)	48 (40 %)	95 (39.6%)			
	Divorced	8 (6.7%)	14 (11.7%)	22 (9.2%)			
	Widow	2 (1.7%)	4(3.3%)	6 (2.5%)			
	Total	120(100 %)	120(100 %)	240 (100 %)			
Education level	Illiterate	12 (10 %)	39 (16.3%)	39 (16.3%)	7.84	4	0.098
	Primary	21 (17.5%)	44 (19.3%)	44 (19/3%)			
	Middle school	30 (25 %)	55 (22.9%)	55 (22/9%)			
	High school	44 (36.7%)	80 (33.3%)	80 (33/3%)			
	Collegiate	13 (10.8 %)	22 (9.2%)	22 (9/2%)			
	Total	120(100 %)	120(100 %)	240(100 %)			
Age	15-25	7 (5.8 %)	23 (19.2%)	30 (12.5%)	11.195	4	0.024
	26-35	45 (37.5%)	44 (36.7%)	89 (37.1%)			
	36-45	34 (28.3%)	24 (20 %)	58 (24.2%)			
	46-55	18 (15 %)	18 (15 %)	36 (15 %)			
	55>	16 (13.3%)	11 (9.2%)	27 (11.3%)			

	Total	120(100 %)	120(100 %)	240(100)			

The results showed that the distribution of gender, education level and marital status, with the probability of (p = 0.611, p = 0.391, p = 0.098) are identical between the two groups. The age distribution was not similar between the two groups (p = 0. 024).

Table 2. Descriptive analysis and the results of comparing the following variables between the two groups of consumers of typical and atypical drugs.

Variable	Drug	N	Mean	Standard deviation	Mean of scores	Mann-Whitney U	**P Value**
Age	Perphenazine	120	(36.72%)	12.4	109.54	13144.5	0.014
	Risperidone	120	(39.87%)	11.238	131.46		
Pr^1	Perphenazine	120	0.1467	0.0239	117.13	14056	0.399
	Risperidone	120	0.1497	0.0256	123.87		
Qt^1	Perphenazine	120	321.33	35.526	114.58	13749.5	0.156
	Risperidone	120	328.25	36.75	126.42		
Hr^1	Perphenazine	120	82.56	17.282	116.21	13945.5	0.336
	Risperidone	120	86.31	21.186	124.79		
Pr^2	Perphenazine	120	0.1467	0.0255	118.23	14188	0.575
	Risperidone	120	0.1503	0.0323	122.77		
Qt^2	Perphenazine	120	324	35.702	114.85	13781.5	0.176
	Risperidone	120	330.92	37.146	126.15		
HR^2	Perphenazine	120	82.36	15.98	116.46	13975	0.364
	Risperidone	120	85.03	18.85	124.54		
PR^3	Perphenazine	120	0.1470	0.0254	118.67	14240.5	0.651
	Risperidone	120	0.1503	0.0323	122.33		
QT^3	Perphenazine	120	325	35.76	114.71	13765	0.169
	Risperidone	120	332.25	37.44	126.29		
HR^3	Perphenazine	120	82.36	15.883	116.40	13968	0.358
	Risperidone	120	85.16	18.627	124.60		
QTC^1	Perphenazine	111	320.0008	36	108	5800	<0.0001
	Risperidone	114	227	36	117		
QTC^2	Perphenazine	113	323	36	111.04	6107	<0.0001

	Risperidone	117	330	37	119		
QTC[3]	Perphenazine	114	324	36	110	6089	<0.0001
	Risperidone	116	332	37	120		

comparing the average of each of the factors PR1, PR2, PR3, HR1, HR2, HR3, QT2, QT3, QTc 1g, QTc 2g, QTc 3g between the two groups receiving typical and atypical drugs, using Mann-Whitney, Showed that In total, the averages of all variables in the group received perphenazine were more than the group received risperidone. Average QTc1g, QTc2g and QTc 3g between the two groups receiving were significantly different (p <0.0001). The average of all three QTc g, (QTc1g, QTc 2g, QTc3g) in the group received risperidone were significantly more than the group received perphenazine (Table 2).

Table 3. Compares the average of the following variables in any of the typical and atypical drug consumer groups and the whole sample.

Drug	Variable	N	Mean score	Friedman statistics	DF	P Value
Perphenazine	Pr_1	120	2	0.100	2	0.951
	Pr_2		2			
	Pr_3		2.01			
	Qt_1	120	1.92	10.211	2	0.006
	Qt_2		2.02			
	Qt_3		2.06			
	Hr_1	120	2.04	10.050	2	0.592
	Hr_2		1.98			
	Hr_3		1.99			
Risperidone	Pr_1	120	2	0.000	2	1
	Pr_2		2			
	Pr_3		2			
	Qt_1	120	1.92	7.46	2	0.024
	Qt_2		2.02			
	Qt_3		2.06			
	Hr_1	120	2.10	6.837	2	0.033
	Hr_2		1.94			
	Hr_3		1.96			

The whole sample	Qtc_1	223	1	23.021	2	<0.0001
	Qtc_2		2.06			
	Qtc_3		2.09			

The results showed that in the group received perphenazine, the mean of PR and HR factors during the three times, were not likely to have statistically significant difference (p =0.592, p = 0.951).But in the case of QT, in the group received perphenazine, in the three time points, the difference was statistically significant (p = 0.006).That is, the mean QT in the first, second and third times is different, and the difference is in such a way that the average was being increased during the execution of the study (Table 4). The results of comparing the average of each of the factors PR and HR and QT over three time points in the group received risperidone, showed that in the group received risperidone, the average of each of the factors QT and HR during the three checked times was statistically different (p = 0.033, p = 0.024). In the case of QT, the differences are such that the values of this factor in the study were being increased. But in the case of PR, in the group received risperidone, the averages of three time points were not statistically significant (p = 1.000). This means that the average of PR between first and second and third times is not different. A comparison of the mean of QT for all subjects and at three time points, showed that statistically, the mean of QT at three time points are quite different (p <0.0001). This differences suggests that during the study and at three time points, the values of this factor were increased (Table 3).

CONCLUSION

This study aimed to compare of the effect perphenazine and risperidone drug on electrocardiographic in patients with schizophrenia referred to Farabi Hospital in Kermanshah in 2015-2016. The results showed that 4 patients had long PR and 3 had inverted T, which were seen in the ECG after 4 and 8 weeks. 4 people had long PR, 1 person was taking perphenazine and 3 persons was taking risperidone. Also, by analyzing the data, the PR of perphenazine and risperidone consumers were not significantly different, and this was in accordance with the findings of Germana et al (2014), which demonstrated that there is no difference between aripiprazole and risperidone consumers (n=60) [1]. This finding was inconsistent with the findings of Nelson et al. (2009), which was performed on 37 patients treated with sertinidol and reported that significant changes were seen in T waveform [8]. Another finding was that the QT and QTc in consumers of both perphenazine and risperidone was significantly increased. The increase was higher in the risperidone consumers and the difference between the first and second ECGs data was more compared to the second and third ones. QTc2 and QTc3 in risperidone consumers were abnormal in one persons (480 ms), and that was seen at week 4 and week 8. Of course, all of this increases were normal, except one mentioned case. The findings were in line with the study of Germana et al (2014). In this study, a slight increase in QTc was seen in risperidone consumers, but not in aripiprazole consumers [8]. The study Leung et al (2012), showed that consumers of thioridazine, chlorpromazine, haloperidol and droperidol (the first generation drugs), and ziprasidone, risperidone, olanzapine, quetiapine (the second generation drugs), have long QT [8]. In this study, a large number of typical and atypical drugs have been used, but the percentage of long QT is not mentioned. In the study of Manini et al (2014), 472 patients received two types of antipsychotics from one class and 7.12 percent showed long QTc. This finding is inconsistent with current research that may be due to a greater number of samples and the simultaneous use of two antipsychotics [16]. In another study, Yuji ozeki et al (2010) evaluated 1017 patients with schizophrenia; 265 patients received one antipsychotic and other were given other types of drugs. The prevalence of long QT was 2.5%. Taking chlorpromazine, haloperidol and sultopride was associated with long QT. But second-generation antipsychotics, such as olanzapine, quetiapine and risperidone, mood stabilizers and benzodiazepines did not increase QT [17]. In

this study the sample size was more than our study and also different drugs had been used. Another finding of this study was that the QTc1, QTc2 and QTc3 were significantly different between men and women, and in women, the increase was greater. This finding is consistent with the study of Christoph u Correll et al. (2011). In this study, 16 patients with long QT (440ms) were evaluated. The mean QT in females was higher than males [18]. In another study by EitanNahshoni et al (2010), 33 patients with schizophrenia were evaluated and no relationship was seen between age, sex, disease duration and dose of antipsychotics and QT and QTc interval [19]. This finding was inconsistent with the findings of this study.

We conclude that in this study, significant ECG changes were observed in risperidone consumers. Although a small number of patients had abnormal ECG changes, but if study with larger sample size, and evaluation of ECG in longer intervals after treatment, electrocardiogram changes will be more likely. If further studies in this field, it appears that risperidone in patients with heart disease should be prescribed with caution. It is recommended that future studies to be done with larger sample sizes, and also, Electrocardiogram be carried out with longer intervals from the treatment time or it could be performed periodically at regular intervals.

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