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Effect of sertindole on QTc interval in patients with schizophrenia

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ABSTRACT

Sertindole has been marketed and offered daily clinical practice only for 9 months in our country, so no data has been its QTc prolongation potential. In the present study, we performed a clinical trial to investigate the effects of sertindole on QTc in patients with schizophrenia. The study comprised 21 patients with schizophrenia. Sertindole was administered in the following dosing regime: treatment was initiated with 4 mg/day sertindole. From day 3 to day 6, the dose was increased to 8 mg/day, and up to day 9, it was raised to 12 mg/day. The protocol allowed up to dose of 20 mg/day according to effectiveness and tolerability. QTc values were determined at beginning, months 3 and 6. In addition, Positive and Negative Syndrome Scale (PANSS) were scored concomitantly. At the beginning of 6-month period, the mean QTc interval of patients was 391.7 ± 19.2 ms. At the end of this period, it was 402.8 ± 23.8 ms. Although the mean QTc interval changing was significant throughout 6-month period, of the patients, at any evaluation point, only 1 female (451 ms) and 1 male (433 ms) had borderline prolongation at month 3 for both, without any exceeding the dangerous limits. In summary, our results suggest that sertindole is tolerable and despite dose-related QT prolongation, sertindole had not the proarrhythmic profile. Future studies with larger sample evaluating the effects of treatment are required.

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Sertindole is a non-sedating atypical antipsychotic agent with high selectivity for dopaminergic neurons in the mesolimbic system and also with affinity for serotonin 5-HT2A and 5-HT2C, and alpha1-adrenoreceptors [9]. In clinical trials, greater efficacy of sertindole compared to placebo has been shown for both the positive and negative symptoms of schizophrenia [9]. The QT interval is an electrocardiographic (ECG) measure that consist of both some depolarization and repolarization periods of heart, beginning with the onset of ventricular depolarization (Q wave) and ends with completion of repolarization (T wave). In clinical practice, its corrected form for heart rate [corrected QT (QTc)] is used, since the QT interval shortens with arising heart rates. However, it is important to notice that QTc interval prolongation is a warning, not the risk itself. Prolonged QTc interval increases the risk of cardiac arrhythmias, and is an important issue with regard to psychotropic medication including antidepressants beyond antipsychotics. In a cohort study, Henessy et al. [5] from over 90,000 patients with schizophrenia with four antipsychotic drugs: clozapine (9%), haloperidol (43%), risperidone (23%), thioridazine (25%) reveals that these patients have a two- to threefold higher risk of cardiac arrest and ventricular arrhythmia than control group. In the same investigation, there was a dose-dependent relationship between thioridazine and arrhythmic events. This prolongation may predispose to the development of ventricular tachyarrhythmias such as torsades de pointes (TdP) and ventricular fibrillation [11]. In general, drug-induced arrhythmias are more likely to occur in patients with pre-existing QT prolongation, which may be congenital or caused by myocardial disease, starvation, alcoholism, ischaemia, left ventricular hypertrophy, or electrolyte abnormalities such as hypokalaemia [6,8]. Therefore, clinicians should be aware of this side effect, especially for the patients at risk. The relationship between the use of antipsychotic drugs and increased QTC and TdP is established for thioridazine, however, other drugs such as haloperidol could prolong QT and lead to TdP. Sertindole caused to occur a new area of discussion, leading to QT prolongation and possible sudden death [12]. Sertindole has been marketed and offered daily clinical practice only for 9 months in our country. It has been reported that drug-induced QTc changes may vary between Africans and Caucasians, however, only few studies have been reported in other ethnic groups [10,13,15]. In the present study, we performed a clinical trial to investigate the effects of sertindole on QTc in patients with schizophrenia.

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The study consists of 21 patients with schizophrenia (mean age: 27.3 ± 5.8 years) who had applied to Firat University School of Medicine Department of Psychiatry and had been diagnosed with schizophrenia according to DSM-IV. All procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects.

Each patient underwent a detailed diagnostic evaluation by one trained psychiatrist. The patients with any kind of comorbid psychiatric disorder were excluded. All patients were free of all medications at least in the previous 2 weeks. None of the study participants was receiving either vasoactive or psychotropic (e.g., antipsychotics, anxiolytics) agents, and none had alcohol and/or drug abuse or dependence. The participants were excluded if they had current or previous evidence of congestive heart failure, a recent (≤2 months) myocard infarctus, history of percutaneous trans-cardiac angiography, another significant cardiac condition (including cardiomyopathy, valvular heart disease, arrhythmias, a pacemaker, left bundle-branch block or Wolff–Parkinson–White syndrome), a resting blood pressure higher than 180/120 mmHg, a resting left ventricular ejection fraction <30%, a left main artery stenosis ≥50%, a serious pulmonary condition, a severe systemic illness (e.g., cancer) or a noncardiac medical illness that could influence autonomic functioning (e.g., epilepsy).

The sertindole was administered in the following dosing regime: treatment was initiated with 4 mg/day sertindole. From day 3 to day 6, the dose was increased to 8 mg/day, and up to day 9, it was raised to 12 mg/day. The protocol allowed up to dose of 20 mg/day according to effectiveness and tolerability.

In order to reduce emotional distress or state anxiety during the ECG recording, all recordings were performed in the same quiet room during spontaneous breathing, following 10 min of adjustment in the supine position. Moreover, in an attempt to avoid the possible influence of diurnal variations, all the recordings were performed between 09:00 and 12:00 h.

Positive and Negative Syndrome Scale (PANSS) [1,2] was scored concomitantly.

A 12-lead surface ECG was obtained from all subjects in the supine position by using Nihon Kohden (Tokyo-Japan) machine at beginning, months 3 and 6. All patients were breathing freely but not allowed to speak during the ECG recordings. The ECGs were recorded at a paper speed of 50 mm/s. Three leads were recorded simultaneously. Two investigators without knowledge of patients' clinical status measured the QTc manually. The QT interval was measured from the beginning of the Q wave to the end of the T wave.

Statistical analysis was performed using the statistical package for social sciences (SPSS/PC 9.05 version, 1998). In the statistical analysis, paired *t*-test and Pearson's method of correlation were used. Differences were considered significant at $p < 0.05$ for all these tests.

A total of 21 patients (12 males and 9 females) were included into the study. The mean duration of illness for the patient group was 10.68 ± 5.12 years. All were schizophrenic (Table 1). Average daily sertindole dose was 14.7 ± 4.6 mg/day. At last visit, 10 of the patients was receiving 12 mg/day, 8 was receiving 16 mg/day and 3 had on 20 mg/day of sertindole treatment. Except for three patients, none received additional drug. Of the three, for insomnia, two had on diazepam of 5 mg/day, while one had on clonazepam of 2 mg/day in addition to sertindole treatment. Among the patients, 61.9% were smokers. All patients completed the study period, except one who did not come to visit month 6.

At the beginning of 6-month period, the mean QTc interval of patients was 387.7 ± 19.2 ms. At the end of this period, it was 402.8 ± 23.8 ms. The difference was statistically significant ($p < 0.05$). The maximum QTc interval was 442 ms in a male patient.

Table 1
Participants characteristics

Patients ($n = 21$)	
Age (years)	27.3 ± 5.8
Sex ratio (F/M)	9/12
Duration of illness (years)	10.7 ± 5.1
Average daily sertindole dose (mg/day)	14.7 ± 4.6
Sertindole dose [at last point] (mg)	
12	9
16	10
20	2
PANSS (at last point)	74.9 ± 6.1
Smoking status	
Smoker	13
Non-smoker	8
QTc	
At beginning	387.7 ± 19.2
Month 3	398.1 ± 12.5
Month 6 (for 20 patients)	402.8 ± 23.8*

PANSS, Positive and Negative Symptom Scale; F, female; M, male. *$p < 0.05$, compared to beginning value.

The mean QTc interval for males (396.6 ± 13.4 ms) was lower than that of females than that for males (409.3 ± 17.2 ms) with no statistically significant difference ($p > 0.05$). No torsades de pointes or any arrhythmic events developed. Of the patients, at any evaluation point, only 1 female (451 ms) and 1 male (433 ms) had borderline prolongation at month 3 for both. The mean QTc of the patients who smoked was 405.3 ± 16.2 ms while that of those who did not smoke was 399.5 ± 11.8 ms, with no statistically significant ($p < 0.05$).

QTc values of the patients did not correlate significantly with their PANSS scores (74.9 ± 6.1, at last point), age, or other demographic data. Significant correlation was found between QTc interval and dose ($r = 0.54$, $p > 0.05$).

The present study represents the first examination of sertindole-induced QT prolongation in a local Turkish sample. Although the mean QTc interval changing was significant throughout 6-month period, of the patients, at any evaluation point, only 1 female (451 ms) and 1 male (433 ms) had borderline prolongation at month 3 for both, without any exceeding the dangerous limits.

Antipsychotics-induced QTc prolongation has been taken attention since two deaths due to high dose thioridazine [7]. Thioridazine seems to be have the most severe risk in regard to QTc prolongation and related possible torsades de pointes. However, no antipsychotic currently in use does not seem innocent regarding the risk of QTc interval prolongation. A variety of antipsychotics such as haloperidol, quetiapine, olanzapine, sertindole, and ziprasidone have been blamed the risk of torsades de pointes or cardiac adverse events [3,4]. The general opinion is that the drug-induced QTc prolongation may be related to an increased risk of torsades de pointes which was first demonstrated for thioridazine in huge doses. The same condition was also reported for haloperidol, causing only minimal QTc prolongation. Nevertheless, there are no cases in literature for torsades de pointes related to use of olanzapine, quetiapine, risperidone, and ziprasidone. Ziprasidone causes to the QT prolongation, but there is no evidence to suggest that this leads to torsade de pointes or sudden death. Interestingly, Hennessy et al. [5] implicated that risperidone might be associated with a significantly higher risk of arrhythmic events and death when compared to haloperidol, clozapine, and thioridazine. In our present study, beyond no observation of torsade de pointes, On the other hand, pharmacological effects of the drugs including antipsychotics may be influenced by inherited genotypes and may demonstrate difference between ethnic groups including basic

pattern and drug-induced ECG changes. In regard to this, several investigators implicated drug-induced QT changes in the interval between Africans and Caucasians, with few studies in other ethnicities [10,13,15]. A recent report by Shin et al. [13] suggested that Korean subjects were less sensitive to quinidine-induced QT prolongation than Caucasian subjects. Although the mean QTc interval changing was significant throughout 6-month period, of the patients, at any evaluation point, only one female (451 ms) and one male (433 ms) had borderline prolongation at month 3 for both, without any exceeding the dangerous limits. It seems that a patient behavior to drug in regard to QTc prolongation can be considered as being individual beyond ethnicity. In this subject, Tay et al. [14] proposed that the CYP1A21F polymorphism may contribute to the risk of developing prolonged QT interval in patients who are treated with higher doses of antipsychotics.

The main limitation of the present study is sample size. Second, no control group was not used. In future studies, other atypical antipsychotics especially olanzapine, ziprasidone can be investigated in comparison with sertindole. Finally, the nature of the sample obtained (e.g., restrictive inclusion/exclusion criteria) might have potentially lessen the generalizability of the results. In summary, our results suggest that the sertindole is tolerable and despite dose-related QT prolongation, sertindole had not the proarrhythmic profile. Future studies with larger sample evaluating the effects of treatment are required.

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