Arrhythmic Markers and Clozapine in Patients with Schizophrenia: Effect of 10 weeks Clozapine Treatment on Heart Rate Variability, Late Potentials and QT Dispersion

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ÖZET:
Şizofreni hastalarında klozapin ve aritmi belirleyicileri: Ön haftalık klozapin tedavisinin kalp hızı değişkenliği, geç potansiyeller ve QT dispersiyonuna etkisi

Amaç: Klozapin özellikle tedaviye dirençli şizofreni hastalarında çok faydalı, iyi bilinen atipik antipsikotik bir ilaçtır ancak aritmi ve ani ölüm riskine yol açma olasılığı hala tartışmalıdır. Şizofreni hastalarında klozapinin aritmi belirleyicileri üzerine etkisini araştırmak amacıyla, 10 haftalık tedavi öncesi ve sonrasında kalp hızı değişkenliği, QT dispersiyonu ve geç potansiyeller ölçüldü.
Yöntem: Kalp hızı değişkenliği ve QT dispersiyonu elektrokardiyografi ile, geç potansiyel ölçümleri, sinyal ortalamalı elektrokardiyografi ile yapıldı. Kalp hızı değişkenliği, QT dispersiyonu ve geç potansiyeller başlangıçta, en az 2–7 günlük ilaçtan arınma döneminin ardından ve 10 haftalık klozapin tedavisi sonrasında yapıldı.
Bulgular: Geç potansiyeller ve QT dispersiyonu ya da düzeltilmiş QT değerlerinde tedavi öncesi ile sonrası arasında fark saptanmadı. Kalp hızı değişkenliğinde tedavi sonrasında istatistiksel olarak belirgin derecede düşme saptandı. Kadın hastalar ve 35 yaşın altındaki hastalarda bu fark daha belirgindi. Kalp hızı değişkenliği ortalama değerindeki düşme klozapin dozu ile istatistiksel olarak anlamlı derecede ilişkili ancak sersemlik, hipertansiyon, azalmış terleme gibi yan etkilerle ilişkisiz bulundu.
Sonuç: Klozapin, 10 haftalık tedavi sonrasında kalp hızı değişkenliğinde azalmaya yol açmıştır ve bu etki doza bağımlı olabilir. Bu çalışmada klozapinin aritmi belirleyicileri olan geç potansiyeller ve QT dispersiyonuna etkisi olmamıştır.

Anahtar sözcükler: Şizofreni, klozapin, kalp hızı değişkenliği, geç potansiyeller, QT dispersiyonu

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ABSTRACT:
Arrhythmic markers and clozapine in patients with schizophrenia: effect of 10 weeks clozapine treatment on heart rate variability, late potentials and QT dispersion

Objective: Clozapine is a well-known atypical antipsychotic agent which is especially useful in patients with treatment-resistant schizophrenia, but there is still debate on its potential to cause arrhythmia and sudden death. To explore the effect of clozapine on arrhythmic markers in patients with schizophrenia, heart rate variability, QT dispersion and late potentials were measured before and after 10 weeks' treatment.
Method: Heart rate variability and QT dispersion were measured by electrocardiography. Signal averaged electrocardiography was used to measure late potentials. Heart rate variability, QT dispersion and late potentials were measured at baseline with at least 2-7 days wash-out period and after 10 weeks of clozapine treatment.
Results: No significant differences were found in late potentials and QT dispersion domains or QT corrected values between pretreatment and posttreatment parameters of clozapine. Heart rate variability measures seemed to be significantly decreased after the treatment. This difference was more prominent in female patients and patients who were under 35 years. Change in mean heart rate variability value was found to be significantly correlated with the dosage of clozapine but not with autonomous side effects such as dizziness, hypertension, and decreased perspiration.
Conclusion: Clozapine decreases heart rate variability after 10 weeks of treatment and this effect may be dose dependent. In this study, clozapine did not effect late potentials and QT dispersion as markers of drug-induced arrhythmia.

Key words: Schizophrenia, clozapine, heart rate variability, late potentials, QT dispersion

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INTRODUCTION

Clozapine is a well-known atypical antipsychotic agent which is very useful especially in patients with treatment-resistant schizophrenia but there is still debate on its potential to cause arrhythmia and sudden death (1). QT prolongation and cardiomyopathy are two mostly reported cardiac side effects of clozapine therapy related with sudden cardiac death (2,3).

However, benign electrocardiographic abnormalities have also been detected due to clozapine treatment (4). The proposed elevated risk of sudden cardiac death in patients with schizophrenia justifies efforts to assess the arrhythmogenic property associated with antipsychotic medication (5,6).

Heart rate depends on the influence of sympathetic and parasympathetic activity on the sinus node (7). Heart rate

variability (HRV) shows the variation in the cardiac interbeat interval over time and is assessed by analyzing a time series of beat-to-beat intervals from continuous electrocardiogram (ECG) recordings (7). Various measures of HRV have been proposed which can roughly be subdivided into time domain, frequency domain and non-linear measures (8). HRV reflects spontaneous changes in autonomic activity and it has been shown to be a sensitive parameter reflecting central autonomic control of cardiac function (8). Alterations of HRV indicating a shift of the autonomic balance to the parasympathetic activity's disadvantage have been connected with an elevated risk of mortality and arrhythmic complications (9,10). Abnormalities of HRV have been described in several conditions such as ischemic heart disease, cardiac failure, diabetes mellitus and also in anxiety disorders (11). HRV measuring has become a potentially useful tool for the assessment of pharmacological modulation of cardiac autonomic function (12).

Clozapine demonstrates a broad range of receptor binding profile, including strong antimuscarinic properties and simultaneous α-1 and α2-adrenoreceptor antagonism thus is very likely to cause changes in central autonomic control of heart rate (13). There are a number of studies showing strong effects of clozapine on HRV parameters: Zahn and Pickar found that clozapine treatment along with changing peripheral indicators of autonomic nervous system, increased heart rate and decreased HRV in patients with schizophrenia indicating cardiovascular autonomic neuropathy (14). Agelink found that clozapine treatment of 100 mg/day for two weeks reduced HRV significantly and this effect was interpreted to be the result of reduced resting parasympathetic tone (15). HRV was also proposed to be useful as a predictor for plasma clozapine levels as the reduced HRV parameters were found to be negatively correlated with the plasma clozapine levels (16). Like clozapine, olanzapine was shown to decrease HRV measures due to anticholinergic side effects, but the effect of clozapine was found to be more prominent and dose dependent (17,18). Silke et al studied the effects of other antipsychotics as well: single doses of thioridazine, risperidone and olanzapine were tested for their effects on HRV and

were found to decrease, not to affect and to increase HRV respectively but the subjects were healthy male volunteers (19). Clozapine was compared to other antipsychotics by means of HRV and it was found that heart rate was significantly higher and HRV was significantly less in schizophrenia patients taking clozapine than in patients taking either haloperidol or olanzapine and in healthy control subjects (20,21).

HRV measurement studies in untreated patients with schizophrenia report increased heart rate and decreased HRV compared to control subjects (15,22). Besides antipsychotic treatment, psychotic symptoms were also found to be related to inhibition of autonomic function and decrease in HRV (23,24).

Late Potentials (LPs) are low amplitude electrical signals detected by the signal averaged ECG (SAECG) and occur after the normal QRS and represent delayed conduction in ventricular myocardium. Since delayed conduction in ventricular myocardium represents the substrate necessary for electrical re-entry -the cause of most episodes of ventricular tachycardia-, LPs are associated with increased risk of ventricular tachyarrhythmias and sudden cardiac death (25). The most commonly demonstrated use for assessment of LPs with SAECGs is their ability to predict the likelihood of ventricular tachycardia and fibrillation in post myocardial infarction period (26). LPs are also used to identify medication related arrhythmogenicity and tricyclic antidepressant treatment has been reported to induce LPs indicating a risk for ventricular arrhythmias. However according to our knowledge there is no study that evaluates LPs after antipsychotic treatment (27).

QT interval dispersion (QTd) is a measure of interlead variations of the surface 12-lead ECG and is a non-invasive measurement for quantifying the degree of myocardial repolarization inhomogeneity (28). Increased QTd, found in various cardiac diseases such as myocardial infarction, long QT syndrome and drug arrhythmogenicity reflects cardiac instability and is associated with increased risk for cardiac death (28). Along with prolongation of QTc –heart rate corrected QT interval- in the ECG recordings, QTd gained particular attention as a marker of drug-induced arrhythmia in patients with schizophrenia but up to date no study about the effects of clozapine treatment

on QTd has been published (29,30).

In this present study, HRV, QTc, QTd and LPs measurements were compared in patients with schizophrenia before and after 10 weeks of treatment with clozapine. The aim was to estimate the risk of drug-induced arrhythmia associated with clozapine.

MATERIALS and METHODS

Subjects

The study included inpatients and outpatients diagnosed with schizophrenia by DSM-IV criteria (31), 18 to 55 years of age, who were non-responsive to at least two different types of antipsychotics. Non-responsiveness was defined as failing to respond adequately, i.e., having persistent positive symptoms, to at least 2 trials of antipsychotic treatment other than clozapine. All of the patients were non-responsive but not treatment resistant because they did not fulfill the strict treatment resistant criteria with regard to dosage (32). The study was approved by the local ethics committee and all of the patients gave written informed consent.

The patients were included unless medical history, all available clinical data and physical exam revealed a physical illness or a history of any cardiovascular or medical illnesses such as diabetes mellitus, hypertension and coronary heart disease. The patients who had a depot antipsychotic injection within the last month and alcohol and substance use disorder within the last three months were excluded.

Two patients were excluded from the study; one for having diabetes mellitus and another having a depot antipsychotic injection within the last month. One patient were not included as he refused to take part in the study.

Sixteen patients (5 men and 11 women) with a diagnosis of schizophrenia were included in the study.

Table 1: Patient characteristics

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Age	36.44 (11.50)
Sex (male)	5 (31.25%)
Mean age at onset of illness (year)	22.8 (5.76)
Mean duration of illness (year)	13.62 (8.98)
PANSS before treatment	87.50 (17.49)

Values are presented as mean(standard deviation)

PANSS: Positive and Negative Syndrom Scale

The patients had a mean age of 36.4(±11.5) years with a range of 20-56 and a mean duration of illness 13.6(±9.0) years with a range of 1-28. The mean age of onset of illness was 22.8(±5.8) years (Table 1).

Cardiac and clinical assessments

Echocardiographic examination was performed on all of the patients before entering the study to make sure that none of the patients have any abnormal systolic or diastolic functions.

HRV, QTc and QTd were measured by electrocardiography. Signal averaged electrocardiography was used to measure LPs. HRV, QTc, QTd and LPs were measured at baseline. QTd was calculated as the difference between the maximum and minimum QT intervals on any standard 12-lead ECG. All electrocardiographic measurements were done by an experienced cardiologist (Ö.K.).

After a wash-out period of 2-7 days for each patient, clozapine treatment was instituted by 12.5 mg/day and the dosage was increased to 50-100 mg/day at the end of first week and to 200, 400 and 600 mg/day at the end of second, third and fourth weeks respectively as far as the patient could tolerate. Mean clozapine dose at the end of 10th week was 465.62(±205.52) mgr/day. Only diazepam (5-15 mg/day, used in 7 patients) were allowed as concomitant drug therapy. After 10 weeks of clozapine treatment HRV, QTc, QT dispersion and LP measurements were repeated.

In order to evaluate severity of schizophrenia symptoms and efficacy of clozapine treatment PANSS (Positive and Negative Syndrome Scale) (33) was performed by weekly. PANSS is a 30-item rating scale which is a drug sensitive instrument for assessing positive and negative symptoms and general psychopathology in schizophrenia.

UKU (Udvalg for Kliniske Undersogelser) side effects rating scale (34) was also performed at each week to assess the side effects related to clozapine treatment such as difficulty in accommodation, increased salivation, orthostatic dizziness, palpitation, increased perspiration, hypertension, weight gain or loss. UKU scale is an instrument built to reveal the adverse events related to psychotropics and is composed of four subscales to measure the presence and severity

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of psychic, neurological, autonomic and other side effects on a 0 to 3 scale. PANSS and UKU ratings were collected by the investigators in the study (M.N.T., B.B.A.) who are experienced in both instruments. The ratings throughout the study for a given patient were performed by the same rater.

Statistical Analysis

Statistical comparisons between baseline and 10th week measures were performed with Wilcoxon Signed Ranks Test. Spearman rank correlation was used to assess the correlation between change in HRV measurements and change in PANSS or dosage of clozapine or autonomous side effects. SPSS 15.0 software was used for data analyses.

RESULTS

A significant decrease in PANSS values were noted after 10 weeks' of clozapine treatment: 87.50±17.49 before and 65.68±19.25 after the treatment (z= 2.79, p=0.005).

After treatment both QT dispersion and corrected QT values increased but the increases were not significant. Late potential values also increased after the treatment but the increases were not significant either (Table 2).

Regarding HRV measures, although SDNN (Mean of the standard deviations of all filtered RR intervals) values decreased after ten weeks' of clozapine treatment, the decrease was not found to be significant but HRVmean and LF/HF (Low to high freqency power ratio) values decreased significantly after treatment (Z= 2.224, p=0.026 and z= 2.225, p=0.026 respectively). Changes in PANSS, QTc, QT dispersion, late potentials and HRV measures before and after clozapine treatment are presented in Table 2.

To explore the effects of age and gender on arrhythmia markers, the patient group was divided by gender and age. When the group was divided as male and female, LF/HF among the HRV measures was found to decrease significantly in the female group by clozapine treatment (Z= 2.851, p=0.004). When the patient group was divided into two as younger as and older than 35 years, LF/HF was again found to be decreased significantly in the younger group (Z= 2.028, p= 0.043).

Correlation analysis revealed that change in HRV mean value was significantly and negatively related to clozapine dosage at the end of ten weeks' treatment (rs= -0.665, p=0.005). Change in HRV mean value was not found to be correlated with change in PANSS or autonomous side effects detected by UKU like disturbance in accommodation, or salivation, orthostatic dizziness, change in perspiration or hypertension.

Table 2: Changes in PANSS, QTd, QTc, Late potentials and HRV measures before and after Clozapine treatment

	Before	After	Z	P
PANSS	87.50 (17.49)	65.68 (19.25)	-2.79	0.005*
QTd (ms)	32.18(10.94)	34.37(12.76)	-0.698	0.485
QTc (ms)	395.6(151.7)	451.2(174.6)	-1.165	0.244
Late potentials				
fQRS (ms)	96.06(9.76)	98.00(8.01)	-1.194	0.232
HFLA (ms)	27.00(7.95)	28.50(7.98)	-0.806	0.420
RMS-40 (ìv)	57.56(40.30)	53.50(42.87)	-0.827	0.408
HRV parameters				
HRVmean (ms)	869.68(365.62)	624.62(130.49)	-2.224	0.026*
SDNN (ms)	258.62(323.36)	228.41(219.90)	-0.284	0.776
LF/HF ratio	1.68(1.09)	1.08(0.84)	-2.225	0.026*

Values are presented as mean (standard deviation).

PANSS: Positive and Negative Syndrom Scale; QTd: QT dispersion; QTc: corrected QT interval; fQRS: Filtered QRS duration; HFLA: Duration of high frequency components in low amplitude; RMS-40: Root mean square voltage in the last 40 ms of the fQRS; SDNN: Mean of the standard deviations of all filtered RR intervals for all 5 min segments of the analysis; LF/HF ratio: Low frequency/High frequency ratio

ms: milliseconds; μv: microvolt

* Wilcoxon Signed Ranks Test, p<0.05

DISCUSSION

Previous studies have shown that clozapine has been associated with HRV reduction (15,20). Also in the present study, clozapine was found to decrease HRV mean and LF/HF measures after 10 weeks of treatment and this effect was profound in female patients and patients under 35. Alterations in HRV measures like HRV mean and LF/HF are considered to be related with the sympathovagal imbalance which is reported to result from clozapine treatment (13,24). The alterations that have been reported in this present study may be related to autonomic side effects of clozapine, which are linked to strong antimuscarinic properties and simultaneous α-1 and α2-antagonism (35). Olanzapine having a less strong anticholinergic effect was also shown to affect HRV but to a lesser degree (18). This study also demonstrated that the amount of change in HRV shows significant negative correlation with the total daily dose of clozapine but not with change in PANSS values or autonomous side effects that are detected by UKU side effect rating scale (34). These results show that HRV is decreased by clozapine treatment in a dose dependent manner.

Although differential effects of antipsychotic medication in subgroups of patients have not been well studied, cardiac effects are reported to be particularly problematic for women (36). Women were reported to have a greater HRV than men and this was suggested to be related with parasympathetic autonomous system being more active in women (37,38). This may represent a state of vulnerability to anticholinergic effects of clozapine and this could be an explanation of our finding. Patients of older age were reported to have an increased risk for all kinds of cardiac side effects (39). In this study HRV alterations were found to be more profound in patients younger than 35 but further studies are needed to elucidate the effect of clozapine on HRV measures on different age groups of patients.

There are a number of studies showing reduced HRV as a result of clozapine treatment in schizophrenia patients in comparison to normal control subjects (20,24). These studies were criticized as patients with psychosis were compared to control subjects and psychotic symptoms besides antipsychotic medications were also blamed to suppress the cardiac autonomic function and decrease in HRV (23). Autonomic dysfunction was also shown in drug-free schizophrenia patients (40). But the exact relation between psychotic symptoms and autonomic dysfunction is not well studied. Kim et al reported that patients with schizophrenia on clozapine had significantly reduced HRV than the control subjects and psychotic symptom severity assessed by PANSS was inversely related with HRV and that was interpreted as a proof for quantitative relation between psychotic symptoms and decreased heart rate dynamics (24).

However in this present study, before and after values of the same patients were compared. This present study also shows that autonomic dysfunction in patients treated with clozapine worsens even when the psychotic symptoms resolves. The results of this study suggest that clozapine per se is involved with autonomic dysfunction.

In the present study clozapine treatment for ten weeks caused increase in QTc and QT dispersion but the increase failed to reach statistical significance. Prolongation of QTc was shown to be associated with blockade of potassium channels of myocardial fibers and delay in the repolarization phase of the action potential (29). Stöllberger et al reviewed the effects of several antipsychotic medications on QT interval and reported significant QTc prolongation associated with clozapine treatment; however the number of patients in this study may be too low to detect a significant difference in QT measures (41).

There are several limitations associated with this study. With regards to the finding that treatment had not changed QTd, QTc and LPs, the number of the patients in the study restricts us to state that clozapine does not cause a change in these parameters. Also, the number of patients in the study did not let us to reveal the exact relation between arrhythmia markers and patient characteristics like age and sex. Although we found a relation between clozapine dose and HRV measures, assessment of the plasma clozapine concentrations might further reveal the correlation between clozapine treatment and arrhythmia markers.

This study showed that clozapine for ten weeks decreased HRV measures in a dose-dependent

manner which might be the result of the autonomic responses induced by clozapine and this effect was profound in female patients and patients under 35 years old. Also in this study, clozapine did not have any negative effect on LPs, QTc and QT dispersion as markers of drug-induced arrhythmia. Due to its

limitations these results can not be generalized to all patients. Further studies with higher number of patients that enables to explore the patient susceptibility characteristics to drug induced arrhythmia are required to explore the precise mechanism of potential cardiac toxicity of clozapine.

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