

Antipsychotic drugs and QT interval prolongation

Antipsihotična zdravila in podaljšanje QT intervala

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Abstract: Objectives. Prolongation of myocardial repolarization, i.e. lengthening of the QTc interval on surface electrocardiogram (ECG), with increased risk of cardiac arrhythmias, has been recognized as a side effect of many drugs. Most first and second generation antipsychotic drugs can cause dose-related prolongation of QTc, although there are important differences in the potency of individual agents.

Subjects and methods. ECGs in 46 patients suffering from schizophrenic disorder and treated with different antipsychotic drugs one week after the admission to the psychiatric hospital were analyzed in this prospective observational study. Heart rate, QT interval and QTc interval were assessed. The average daily dose of prescribed antipsychotic drugs was calculated.

Results. Average QTc interval was 417 msec, only 3 out of 46 (6,5%) patients had QTc over 450 msec and only one patient (2,2%) had QTc over 500 msec. No differences in QTc interval between patients who were treated either with first or second generation antipsychotic drug or with combination of both were found. Female participants had significantly longer QTc interval than male participants ($p < 0,05$).

Conclusions. Results raise the question of the clinical relevance of a single ECG for diagnostics of cardiac complications in schizophrenia patients and suggest the need to conduct ECG monitoring in patients with high risk for cardiac complications during antipsychotic treatment.

Key words: schizophrenia, treatment, antipsychotic drugs, QT prolongation.

Povzetek: Namen. Podaljšanje časa repolarizacije srčne mišice, tj. podaljšanje QTc intervala na površinskem elektrokardiogramu (EKG), s povečanim tveganjem za srčne aritmije, je bilo prepoznano kot neželeni učinek mnogih zdravil. Večina antipsihotičnih zdravil prve in druge generacije lahko povzroči od odmerka odvisno podaljšanje QTc intervala, čeprav obstajajo pomembne razlike glede na posamezno zdravilo.

Preiskovanci in metode. V prospektivni opazovalni študiji je bila opravljena analiza EKG pri 46 bolnikih s shizofrenijo, ki so bili v času enega tedna po sprejemu v psihiatrično bolnišnico zdravljeni z različnimi antipsihotičnimi zdravili. Izmerjena je bila srčna frekvenca, QT interval, izračunan je bil QTc interval. Izračunan je bil povprečni dnevni odmerek antipsihotičnega zdravila.

Rezultati. Povprečni QTc interval je znašal 417 msec, le 3 od 46 (6,5%) bolnikov je imelo QTc čez 450 msec in le pri enem (2,2%) bolniku je bil QTc čez 500 msec. Razlike v QTc intervalih med bolniki, ki so bili zdravljeni z antipsihotičnimi zdravili prve ali druge generacije ali s kombinacijo obojih, niso bile ugotovljene. Prisotna je bila razlika v QTc glede na spol, pri ženskem spolu je bil QTc pomembno daljši ($p < 0,05$).

Zaključki. Glede na rezultate se postavlja vprašanje o kliničnem pomenu le ene meritve EKG pri ugotavljanju srčnih zapletov pri bolnikih s shizofrenijo, pri bolnikih z visokim tveganje za srčne zaplete se svetuje spremljanje EKG tekom celotnega zdravljenja.

Ključne besede: shizofrenija, zdravljenje, antipsihotična zdravila, QT podaljšanje.

Introduction

Individuals with schizophrenia have a 20% shorter life expectancy than the population at large (1) and greater vulnerability to diabetes, hypertension, and emphysema (2, 3). Although the lifestyles of people with schizophrenia may contribute to these illnesses, some of the antipsychotic medications used to treat schizophrenia have been associated with weight gain, the onset of diabetes, increases in lipid levels, prolactin elevation, cataract formation, movement disorders, sexual dysfunction and changes on the electrocardiogram (ECG) (3-5). The use of combinations of antipsychotics may further increase the risk of these side effects (6, 7). Prolongation of the QT interval of the ECG is associated with the development of torsade de pointes (TdP), a ventricular arrhythmia that can cause syncope and may progress to ventricular fibrillation and sudden death (8). Since the QT interval becomes shorter as the heart rate becomes more rapid, the interval duration is usually corrected for heart rate and referred to as the QTc interval. QT is measured in clinical practice and Bazett's formula is used for the calculation of $QTc = QT/\sqrt{RR}$ (in seconds). The average QTc interval in healthy adults is approximately 400 msec, and the risk of TdP increases as the interval lengthens. A QTc interval of 500 msec or greater is considered to be a substantial risk factor for TdP (9, 10).

The signs and symptoms of cardiac arrhythmias can range from none at all to loss of consciousness or sudden cardiac death. Complaints such as lightheadedness, dizziness, fluttering, pounding, quivering, shortness of breath, dizziness, chest discomfort, and forceful or painful extra heartbeats are commonly reported with various arrhythmias. Often, patients notice arrhythmias only after checking their peripheral pulses (8).

Some psychotropic drugs, particularly tricyclic antidepressants (TCAs) and antipsychotic agents are correlated with iatrogenic prolongation of the QT interval of the ECG and with arrhythmias (11-14). SSRIs, most frequently prescribed antidepressant drugs, were also associated with a modest increase in the QTc interval, although to a lesser extent than TCAs, citalopram was associated with more QTc prolongation than most other SSRIs (15).

The aim of our clinical evaluation was to analyze ECGs in patients suffering from a schizophrenic disorder who were treated with different antipsychotic drugs while admitted to the psychiatric hospital.

Subjects and methods

Forty-six patients with acute episode of schizophrenia were included to the prospective clinical evaluation. Patients were hospitalized at psychiatric hospital in 2008 for acute episode of schizophrenia and were treated with different antipsychotic drugs (first generation, second generation or a combination thereof). After 1 week of treatment, ECG was measured. Heart rate, QT interval and QTc interval were assessed. The average daily dose of prescribed antipsychotic drugs was calculated and transformed to chlorpromazine units. Patients receiving antidepressant drugs were not included to the study. Electrolyte disturbances were excluded.

Clinical criteria for schizophrenia were met according to International Classification of Diseases – 10th Edition (ICD-10). Exclusion criteria were neurological diseases and alcohol or other substance dependence. All subjects were treated at University Psychiatric Clinic in Ljubljana, Slovenia.

Analyses were made with the statistical package SPSS (version 15.0).

The Republic of Slovenia Research and Ethics Committee in Ljubljana approved the research protocol (nr. 110/20/02).

Results

Nineteen male and 27 female patients with acute episode of schizophrenic disorder were included to the clinical evaluation, with average age of 45,11 years (range 20-67, $SD = 12,95$) for male and 46,84 years (range 22-69, $SD = 13,84$) for female patients. Average heart rate was 76,9 per minute (range 55-113, $SD = 14,3$).

Average QTc interval was 417 msec, only 3 out of 46 patients had QTc over 450 msec and only one patient had QTc over 500 msec.

13/46 patients received conventional antipsychotic drugs, 25/46 received atypical antipsychotic drugs and for 8/46 patients combination of drugs were prescribed. Average daily dose of received conventional antipsychotic was 595,4 cpu (range 100-1150, $SD = 347,4$), for atypical antipsychotic group 388,2 cpu (range 50-934, $SD = 229,5$) and for group of patient who were prescribed combination of antipsychotic average daily dose was 769,1 cpu (range 100-1417, $SD = 424,9$).

Later on, we compared differences in QTc between female and male participants. Descriptive statistics are presented in the table below.

Table 1. Average QTc, Standard deviation and Range (in msec) for male and female patients.

	<i>M</i>	<i>SD</i>	Range
Male	409,4	16,1	370-434
Female	425,2	44,4	289-542

As demonstrated in Table 1, females exhibited higher QTc interval ($M_F = 425,23$) compared to male patients ($M_M = 409,42$). Interestingly, the dispersion (*SD*) of results was much higher for female participants as well ($SD_F = 44,41$), compared to male participants ($SD_M = 16,11$). We tested statistical significance in mean values between both groups using Mann-Whitney *U*-test, since the data did not meet the criteria for using parametric *t*-test. Test results revealed that the difference between male and female participants was statistically significant ($U = 123,0; p < 0,05$), indicating that female participants have significantly higher QTc interval than male participants.

Furthermore, we were interested in differences in QTc interval between participants, receiving different types of antipsychotic drugs (first generation, second generation or combination). Descriptive statistics for all three groups of participants are presented in Table 2.

Table 2. Average QTc, Standard deviation and Range (in msec) for patients receiving first generation, second generation or combination of antipsychotic drugs.

	<i>M</i>	<i>SD</i>	Range
First generation	407,15	38,31	289-442
Second generation	426,55	37,21	370-542
Combination	413,75	15,05	394-436

We can see in Table 2 that patients receiving first generation antipsychotic medication had the highest QTc interval ($M_1 = 426,55$). On the other hand, patients who were given second generation antipsychotic medication had the lowest QTc interval ($M_2 = 407,15$). We can also see that the dispersion of results (*SD*) was again different for each group of participants. Patients receiving combination of drugs had the lowest dispersion of results ($SD_{Comb.} = 15,05$), whilst patients receiving first generation ($SD_1 = 38,31$) or second generation ($SD_2 = 37,21$) drug had greater dispersion. To investigate the statistical difference between all three

groups, Kruskal-Wallis *H*-test was used. Again, we were forced to use a non-parametric test, since the criteria for using parametric ANOVA was not met. Despite observed (minor) differences between all three groups, test results revealed that the differences in mean QTc were not statistically significant ($\chi^2(2) = 0,937; p = 0,626$).

Discussion

The risk of drug-induced QTc prolongation with TdP arrhythmias raises a dilemma of early detection of the effects of any new chemical entity on cardiac ventricular repolarization. It has become apparent that not only antiarrhythmic drugs but a variety of other agents may aggravate and provoke TdP and sudden death (16, 17). Cardiovascular mortality is higher among schizophrenic patients than in the general population, and it is possible that most unexplained sudden deaths among these patients are due to ventricular arrhythmias for which antipsychotic drugs are either the cause or a predisposing factor (3). Some of the antipsychotic agents carry a high risk of arrhythmias, related to their effects on the QT interval (18, 19). A QTc interval of 500 msec or greater is considered to be a substantial risk factor for TdP, but a study with 6693 patients undergoing 24-hour ambulatory ECG showed that a QTc interval in excess of 440 milliseconds was associated with more than double the incidence of sudden death (20). Average QTc interval in patients undergoing our clinical investigation was 417 msec, only 3 out of 46 patients had QTc over 450 msec and only one patient had QTc over 500 msec, which represents a high risk for sudden hearth events.

The antipsychotic drugs include two major classes, although some authors challenge the straightforward classification of antipsychotics into first generation and second generation groupings. Rather, hierarchies in the different domains should help clinicians to adapt the choice of antipsychotic drug to the needs of individual patients (21). First generation antipsychotic drugs are strong dopamine D2 receptor antagonists while second generation antipsychotics act mainly as serotonin-dopamine antagonists with different antagonistic effect on D2 receptors. The antipsychotic drugs that are most likely to prolong QTc interval are individual phenothiazines and butyrophenones (e.g., haloperidol) carrying a higher risk as compared with some individual second generation antipsychotic drugs, such as quetiapine and olanzapine, which may have a moderate risk, or aripiprazole, possibly showing a lower potential to cause QTc prolongation (22-24). Aripiprazole is a

partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at serotonin 5-HT2A receptors, alpha1, and histamine H1 receptors. Recent study showed that aripiprazole is a low-risk antipsychotic regarding cardiac safety in healthy patients, however, baseline and steady state electrocardiogram is recommended in patients at high risk for torsade due to marked QTc prolongation and lack of data in this group (25). Sertindole, second generation antipsychotic, which is not registered in Slovenia, was reported to have marked effect on QTc prolongation (21, 26). Altogether, the data concerning individual antipsychotic drugs remain difficult to interpret and somehow controversial (27).

It appears that while the most common extrapyramidal side effects of first generation antipsychotic drugs were known from early times, their cardiovascular safety was not properly in the focus of treatment management and most of them would not be approved if submitted under current restrictions and guidelines (5, 28). Patients included to our evaluation were treated with either first (28%) or second generation (55%) antipsychotic drugs, some of them (17%) were treated with the combination thereof, but no statistically significant difference in QTc interval between the groups was found, although QTc interval in the group treated with second generation antipsychotics was the longest, and even though the average daily dose of prescribed antipsychotic drugs in this group was the lowest.

Some studies report that the risk associated with any given antipsychotic agent is increased if it is combined either with any other drug known to prolong the QTc interval and provoke TdP, or with any drug capable of inhibiting the hepatic metabolism of the antipsychotic agent (29-32). The recent study confirmed that antipsychotic polypharmacy is associated with QTc interval, and this effect is mediated by antipsychotic dose. Given the high prevalence of antipsychotic polypharmacy in real-world clinical practice, clinicians should consider not only the myriad risk factors for QTc prolongation in their patients, but also that adding a second antipsychotic drug may further increase risk as compared with monotherapy, so antipsychotic polypharmacy should be avoided (27). Switching to monotherapy, clozapine use and appropriate duration of monotherapy are the best options to avoid antipsychotic polypharmacy (33, 34).

A number of other risk factors are associated with drug induced TdP. These include sex, age, cardiac disease, comorbid electrolyte disturbances such as

serum hypokalemia, metabolic or endocrine abnormalities, CNS insults, toxins, congenital long QT syndromes and factors interfering with drug metabolism and excretion (35-37). Women have longer average QTc intervals at baseline compared with men and are at increased risk of drug-induced QTc prolongation and arrhythmia. It has been reported that around 70% of drug-associated TdP occurs in women (38). Our test results revealed that the difference between male and female participants was statistically significant, indicating that female participants have significantly longer QTc interval than male participants. Also, elderly are frequently exposed to polypharmacy, and with reduced repolarization reserve and the risk for drug-induced QTc prolongation, TdP are higher in this group (10, 39, 40).

The main limitations of our study are small sample size and absence of more measurements. Results of a recent study revealed, that QTc intervals were statistically significantly prolonged after a relatively short term (2-4 weeks) of antipsychotic treatments, compared with baseline. These results reinforce the importance of monitoring risk factors and assessing QTc prolongation at the beginning and throughout treatment with antipsychotics (41).

Our results raise the question of the clinical relevance of a single ECG for diagnostics of cardiac complications in schizophrenia patients. Because of safety measures (42), the need to conduct ECG monitoring in patients at high risk for cardiac complications before and during antipsychotic treatment, especially in patients exposed to polypharmacy is suggested. Also, multidisciplinary approach, including other specialists (e.g. internal medicine, clinical pharmacy etc.) is highly welcomed to deal with this very important problem in a real clinical practice.

Conclusion

In conclusion, physicians prescribing antipsychotic drugs should be aware that these drugs can induce proarrhythmia in individual cases. Circumstances which are necessary for abnormal QT prolongation and TdP to develop should be known. Patients should be monitored with regard to these risk factors before and during drug treatment.

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