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The effect of metilpheniydate, risperidone and combination therapy on ECG in children with attention-deficit hyperactivity disorder☆

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Abstract

Introduction: This study is to investigate ventricular repolarization on electrocardiogram (ECG) in a pediatric population receiving methylphenidate (MPH), risperidone (RIS) and combined therapy.

Methods: A total of 215 patients between 6 and 12 years with ADHD/conduct disorder receiving methylphenidate, risperidone and combined therapy for minimum 3 months and an untreated ADHD group (n = 76) was consecutively included in the study. Twelve lead ECG parameters including mean QT, QTc, T-peak to T-end (TpTe) intervals, TpTe dispersion and TpTe/QT ratio were compared.

Results: QT interval, and QTc, TpTe interval, TpTe dispersion and TpTe/QTc ratio values for groups receiving RIS, MPH and combined therapy were found to be significantly higher than other groups. Moreover, in the combined therapy group TpTe and TpTe/QTc values were higher than the single drug administration groups ($p < 0.05$). TpTe and TpTe/QT ratio was significantly higher in the RIS group compared to that of the MPH group.

Conclusion: These results suggested that combined therapy of these drugs had a more prominent impact on the T wave and RIS could be strongly associated with it.

Keywords: Drugs; ECG; ADHD

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder characterized by age-inappropriate hyperactivity, inattention, and impulsivity [1]. Treatment of children diagnosed with ADHD needs to be quite comprehensive aiming to offer remedy for their behavioral, cognitive and social issues [2]. Methylphenidate (MPH), a member of the psychostimulant group drugs with sympathomimetic effect, is the most commonly preferred agent for the pharmacological treatment of ADHD [3]. The atypical antipsychotic treatment option is risperidone (RIS) which is a derivation of benzisoxasole is an antagonist of both 5-HT2A/2C and D2 receptors [4]. RIS was assumed to be beneficial for the treatment of ADHD with or without a combined psychostimulant [5]. RIS is the first line treatment for preschool children or children with intellectual disabilities diagnosed with ADHD due to the side effects of MPH on irritability and appetite [6]. There is a strong evidence that MPH and RIS are effective in treating ADHD and behavioral disorder combination. However, the increase in the use of these drugs in recent years has raised concerns regarding their side effects.

MPH which is a blocker of catecholamine reuptake shows central effect through dopamine and noradrenaline. A number of studies have shown previously that the sympathomimetic effect of MPH causes an increase in heart rate as well as systolic and diastolic blood pressure [7–9]. Furthermore, psychostimulant drugs have a pro-arrhythmogenic effect associated with sympathomimetic amines. This cardiovascular side effects are dose dependent and can be controlled by dose adjustment [10]. Antipsychotics are known to be associated with QT prolongation on electrocardiogram (ECG) which predisposes an increased risk of the ventricular arrhythmias [11–13].

MPH and RIS may result in sudden cardiac death due to increased cardiac arrhythmogenesis caused by autonomic dysfunction. The most common cause of sudden cardiac

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death depending on the drugs is torsade de point that is polymorphic ventricular tachycardia associated with prolonged QT interval which is potentially mortal. Early diagnosis of high risk patients is possible by using of surface ECG to detect cardiac repolarization heterogeneity through measurement of QT interval and corrected QT interval (QTc) values. Prolongation of the interval between the peak and the end of the T wave (T-peak to T-end [TpTe]) on the 12-lead ECG may represent a new marker of ventricular arrhythmogenesis [14]. There is only a single study in the literature about TpTe and TpTe/QT values in pediatric ADHD patients with ventricular repolarization dysfunction associated with MPH therapy; however, there is no study on RIS and combined drug therapy [15]. Due to the fact, this study aims to investigate TpTe, TpTe dispersion and TpTe/QT ratio in pediatric patients diagnosed with ADHD receiving MPH, RIS and combined therapy.

Methods

Study populations

This prospective, cross-sectional, controlled study included 215 consecutive pediatric patients (mean age = 8.84 ± 2.02 years, range 6–12 years) who were evaluated for ADHD/conduct disorder and from January 2015 to May 2016 by the Pediatric and Adolescent Psychiatry and Pediatric Cardiology Departments of the university hospital. ADHD was diagnosed by the pediatric and adolescent psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [16]. Patients with a diagnosis of ADHD were divided into four groups (untreated (n = 76), MPH (n = 72), RIS (n = 30) and MPH + RIS (n = 37)). Electrocardiogram data of 70 healthy children were also included to the study as a control group which consisted of healthy children with no cardiac defects and arrhythmias who had been admitted due to palpitation, heart murmur or chest pain initially. ECG parameters of all groups were assessed.

In the MPH group, the treatment was initiated on a 0.5 mg/kg/day dose and maximum dose was 1.5 mg/kg/day. The half-life of the MPH is about 3 h. Short-acting methylphenidate was administered 2–3 times/day and ranged between 10 and 60 mg. Long-acting osmotic-release oral system (OROS) MPH dose ranged between 18 and 72 mg. Four patients were given both short and long acting MPH. In the RIS group, the drug was administered in the morning and/or at bedtime. The half-life for the RIS is 3 h and for the metabolite it is approximately 24 h. Initial dose for RIS was 0.25–0.5 mg/day and maximum dose was 2 mg/day.

The patients who had not taken their drug for longer than two consecutive days before ECG were excluded from the study. The patients with a history or symptoms of cardiovascular, pulmonary, endocrine or psychotic disorders were not included in the study. Informed consent was obtained to participate in the study with a protocol approved by the local ethics committee (2015/194).

Electrocardiography

Standard 12-lead ECG was performed for the patients and the controls at a paper speed of 25 mm/s under similar conditions. A Nihon Kohden ECG 1250 Cardiofax S (2009, Tokyo, Japan) device was used at standard velocity and amplitude. Electrocardiography images had 600-dpi resolution and measurements were made on computer by an experienced pediatric cardiologist. Duration of QT intervals was defined in all derivations and average scores were recorded for each group in which the onset of the QRS complex and the return of T wave to baseline were clearly identified. In order to measure QTc, the QT duration was corrected for heart rate based on the Bazett's formula. Also, heart rate, TpTe, TpTe dispersion, and TpTe/QT ratio was calculated. TpTe was measured via the tangent method in precordial leads [17–19]. A tangential line was drawn where the downward curve of the T wave intersected the isoelectric line. The Tp-e duration was calculated by measuring the distance between the two points on the isoelectric line. The difference between the maximum and minimum Tp-e values in the precordial leads was the Tp-e dispersion. Median heart rate and systolic and diastolic blood pressures for all groups were recorded.

Statistical analysis

The data were processed and analyzed using STATA/MP11. Descriptive data are presented as count (%), means and standard deviations. The distributions of continuous variables were investigated by using Shapiro Wilk's normality test and the comparisons were made using one-way ANOVA or ANCOVA (age-adjusted significance because of correlation between age and related variable). Then, post-hoc Tukey test was used to evaluate multiple comparisons. The comparisons between categorical variables were based on the chi-square test. Overall, the p values less than 0.05 were regarded as significant.

Results

A total of 215 patients (45 females, mean age 8.84 ± 2.02, range 6–12 years), 70 healthy subjects (26 females, mean age 9.01 ± 2.04, range 6–12 years) were included in this study. All groups were similar in terms of age and gender (Table 1). While 72 patients received MPH, 30 received RIS and 37 were given a combined treatment. Patients have been receiving regular treatment for minimum 3 months. Mean systolic and diastolic blood pressure values were found to be significantly higher in patients on MPH compared to untreated ADHD group patients, combined therapy group patients and those in the healthy control group (Table 1). Mean heart rate values were significantly higher in all three treatment groups compared to the healthy control group while no statistically significant difference was found between the values of these groups and the untreated ADHD group (Table 1).

Table 1
Demographic, clinical and electrocardiographic measurements of the groups.

		Healthy control	Untreated ADHD	MPH	RIS	MPH + RIS	p value
Age (year)	Mean ± SD (min–max)	9.01 ± 2.04 (6–12)	8.63 ± 1.97 (6–12)	9.03 ± 1.91 (6–12)	8.17 ± 2.28 (6–12)	9.46 ± 1.95 (6–12)	0.070
Gender	F (n, %) M (n, %)	(26–37.1) (44–62.9)	(19–25.0) (57–75.0)	(12–16.7) (60–83.3)	(7–23.3) (23–76.7)	(7–18.9) (30–81.1)	0.062
HR (bpm)	Mean ± SD (min–max)	85.94 ± 17.62 (56–136)	89.34 ± 16.45 (64–136)	95.89 ± 19.13[a] (62–167)	99.60 ± 18.05[a] (65–150)	96.95 ± 18.83[a] (65–150)	<0.001
PR (ms)	Mean ± SD (min–max)	142.29 ± 18.97 (100–200)	136.95 ± 18.96 (90–200)	132.50 ± 19.63[a] (90–170)	128.00 ± 21.72[a] (100–170)	126.76 ± 18.11[a] (90–190)	<0.001
QRS (ms)	Mean ± SD (min–max)	91.29 ± 13.56 (80–120)	96.18 ± 10.95 (80–120)	101.32 ± 13.94[a] (80–120)	100.67 ± 13.88[a] (80–130)	88.38 ± 19.58[b–d] (60–170)	<0.001
Systolic BP (mmHg)	Mean ± SD (min–max)	104.43 ± 9.98 (90–130)	103.96 ± 7.70 (90–120)	109.17 ± 9.71[a,b] (90–130)	108.33 ± 10.93 (80–120)	102.70 ± 9.62[c] (90–140)	0.001
Diastolic BP (mmHg)	Mean ± SD (min–max)	64.50 ± 7.62 (50–90)	66.58 ± 5.55 (60–80)	70.63 ± 8.18[a,b] (50–90)	68.37 ± 7.48 (50–80)	65.54 ± 8.23[c] (50–90)	<0.001

ADHD = attention-deficit hyperactivity disorder; MPH = methylphenidate; HR = heart rate; RIS = risperidone; MPH + RIS = methylphenidate + risperidone; systolic BP = systolic blood pressure.

[a] Different from healthy control ($p < 0.05$).
[b] Different from untreated ADHD ($p < 0.05$).
[c] Different from MPH ($p < 0.05$).
[d] Different from RIS ($p < 0.05$).

Electrocardiographic results

The TpTe, TpTe dispersion and TpTe/QT ratio in all three treatment groups were significantly higher than those in the healthy control group and untreated ADHD group ($p < 0,001$). Furthermore, significant difference was observed with respect to TpTe and TpTe/QT ratio in the treatment groups (Fig. 1). These parameters were significantly higher in patients receiving combination therapy compared to the patients treated with MPH or RIS group alone. TpTe and TpTe/QT ratio in the RIS group was significantly higher than the MPH group (Table 2, Fig. 2).

A statistically significant difference was observed between the groups regarding QT interval and QTc values: They were significantly higher in all three treatment groups compared to both untreated ADHD and healthy control groups (Table 2). Despite of the fact that a statistically significant difference was not observed among the treatment groups, mean QTc values in the RIS group were the highest (448 ± 21.4). There were only three patients with a QTc level > 500 ms. We re-evaluated the treatments of these patients and planned holter ECG to assess arrhythmia. No arrhythmia or ST changes were observed in both groups.

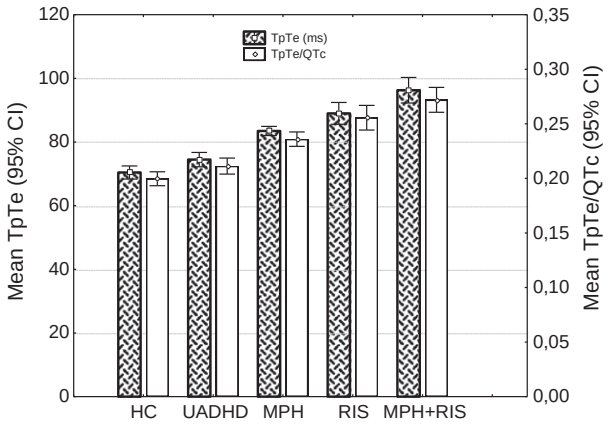

Fig. 1. Mean TpTe and Mean TpTe/QTc values of the groups and healthy controls. ADHD = attention-deficit hyperactivity disorder; HC = healthy control; MPH = methylphenidate; RIS = risperidone; MPH + RIS = methylphenidate + risperidone; UADHD = unhealthy ADHD; TpTe = T-peak to T-end.

Discussion

Stimulants such as MPH have become the mainstream pharmacological treatment for ADHD. The use of RIS alone or in combination with other psychostimulants has increased in the recent years due to its proven benefits in pediatric patients with ADHD [5]. Despite the high level of efficacy for both drugs whether used single or in combination in the treatment of ADHD, the number of concerns raised regarding their side effects. This is the first study comparing electrocardiographic effects of MPH, RIS and combination therapy given to pediatric patients diagnosed with ADHD. The values of QT interval, QTc, TpTe interval, TpTe dispersion and TpTe/QTc ratio in the RIS, MPH and combination therapy groups were significantly higher than both control and untreated ADHD groups. Moreover, in the combination therapy group, TpTe and TpTe/QTc duration was longer than single agent treatment groups. Besides, TpTe and TpTe/QT ratio in the RIS group was significantly higher compared to the MPH group.

In recent years, a number of studies conducted with adult patient groups have proved cardiovascular safety of MPH. However, only a few studies have been conducted with pediatric patients. Stimulants like MPH are known to increase heart rate and blood pressure [7,15]; whereas, these cardiovascular effects do not seem to be severe [9,15]. On the other hand, it is reported that the stimulant drugs such as MPH are pro-arrhytmogenic with HR variability and can possibly be associated with cardiac-dependent sudden

Table 2
Electrocardiographic parameters of the groups.

		Healthy control	Untreated ADHD	MPH	RIS	MPH + RIS	p value
QT (ms)	Mean ± SD (min–max)	354.39 ± 28.62 (300–410)	354.74 ± 31.004 (270–430)	356.67 ± 32.15[a,b] (300–430)	350.00 ± 29.60[a,b] (300–430)	355.41 ± 32.63[a,b] (300–430)	0.011
QTc (ms)	Mean ± SD (min–max)	415.31 ± 24.51 (350–459)	420.00 ± 23.74 (350–465)	444.03 ± 30.39[a,b] (390–520)	448.00 ± 21.44[a,b] (390–500)	433.65 ± 25.59 (370–480)	<0.001
TpTe (ms)	Mean ± SD (min–max)	70.43 ± 8.65 (53–88)	74.47 ± 9.87 (56–120)	83.47 ± 6.13[a,b] (65–100)	89.00 ± 9.17[a,b] (76–115)	96.27 ± 12.06[a,b] (80–120)	<0.001
TpTe_dispersion (ms)	Mean ± SD (min–max)	8.79 ± 1.69 (7–13)	8.45 ± 0.92 (7–11)	9.24 ± 1.27[b] (8–13)	10.63 ± 1.73[a,b,c] (8–14)	9.51 ± 1.30[b,d] (7–12)	<0.001
TpTe/QTc	Mean ± SD (min–max)	0.200 ± 0.027 (0.14–0.25)	0.211 ± 0.032 (0.16–0.34)	0.236 ± 0.028 [a,b] (0.18–0.33)	0.256 ± 0.030 [a,b,c] (0.20–0.33)	0.272 ± 0.034 [a,b,d] (0.21–0.37)	<0.001

ADHD = attention-deficit hyperactivity disorder; MPH = methylphenidate; RIS = risperidone; MPH + RIS = methylphenidate + risperidone; TpTe =T-peak to T-end.

cardiac death [8,15]. As suggested in the literature, mean systolic and diastolic blood pressure values obtained in our study were significantly higher in the MPH group compared to the combination therapy, untreated ADHD and healthy control groups. Mean systolic and diastolic blood pressure values were also slightly higher in RIS group. However, we did not find significantly increased blood pressure values in patients who were treated with combined MPH and RIS. RIS may produce both high and low blood pressure values [20]. This paradoxical effect of RIS on blood pressure along with the unknown drug interactions may explain why the group with combined MPH and RIS treatment did not show high blood pressure values compared to the groups who were treated with these agents separately. School age children diagnosed with ADHD have been known to present low level of parasympathetic tone accompanied by physiological maturation deficiency of the autonomic function that is expected [8]; thus, resulting increased heart rate in the untreated ADHD patient group has also been observed. For all three treatment groups, although we have observed statistically significant increases in mean heart rate values compared to the healthy group, we have found no significant differences between these groups and the untreated ADHD group. It has been assumed that this could be associated with the low parasympathetic tone in ADHD patients.

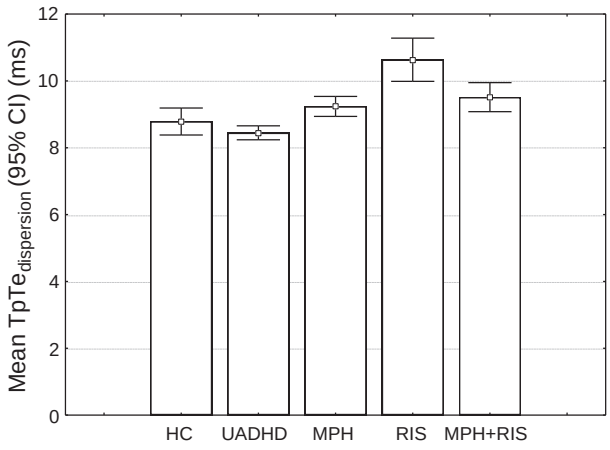

Fig. 2. Mean TpTe dispersion values of the groups and healthy controls. ADHD = attention-deficit hyperactivity disorder; HC = healthy control; MPH = methylphenidate; RIS = risperidone; MPH + RIS = methylphenidate + risperidone; UADHD = unhealthy ADHD; TpTe dispersion = T-peak to T-end dispersion.

Although cardiovascular side effects of antipsychotics predominantly used in ADHD treatment have been unclear, there are still some hypotheses. In vitro studies have shown the relationship between the RIS and the prolonged action potential in human myocardial tissues [21]. It has also been demonstrated that it increases QTc interval duration at different levels in humans causing possible polymorphic ventricular tachycardia and sudden cardiac death [11–13]. There are few studies in RIS treatment for pediatric group patients. In two different studies with pediatric patients, RIS was found to create no difference in QTc values. However, they have their limitations due to the small number of patients (respectively 7 and 12) [22,23] participating in both studies. Geller et al. did not find significant difference in QTc values versus baseline after 8 weeks of therapy in 78 children and adolescents treated with risperidone [24]. However, Germano et al. demonstrated that the treatment with risperidone is associated with a small increase of post treatment QTc values compared to baseline [25]. The meta-analysis by Jensen et al. of 23 studies, 19 of which were randomized, suggests a statistically significant increase in QTc for 1.68 ms in RIS patients [26]. In our study, QT and QTc values were found to be significantly higher in the medically treated groups compared to both untreated ADHD and healthy control groups. Although there was no significant difference between the treatment groups, the highest increase in QTc value occurred in the RIS group. Therefore, we have concluded that the drugs were associated with the increase in QT and QTc levels especially with RIS treatment.

While QT interval duration plays a role in heterogeneous myocardial repolarization, it is not always an accurate predictor for polymorphic ventricular tachycardia (Torsades de points) and sudden cardiac death [12]. As T wave morphology is the predictive marker in drug associated polymorphic ventricular tachycardia, it must be investigated in details. TpTe may be the best predictor for ventricular arrhythmogenesis. This marker was particularly useful when the QTc interval was normal or immeasurable due to prolonged QRS duration [14]. TpTe interval, TpTe dispersion and TpTe/QTc ratio have been novel transmyocardial repolarization parameters defining trans-myocardial

heterogeneity [17–19]. Moreover, some studies have reported that TpTe interval, TpTe dispersion and TpTe/QT ratio are superior to the QT interval and QT dispersion in predicting ventricular arrhythmias [27,28]. TpTe is prolonged in the congenital long QT syndrome and predicts Torsades de points in acquired long QT syndrome [29]. Rosenthal et al. found that TpTe independently predicts both VT/VF and overall mortality in patients with systolic dysfunction and ICDs implanted for primary prevention in their study [28]. A significantly prolonged TpTe correlates with a higher number of sudden cardiac death cases and increased mortality of patients with ST-segment elevation myocardial infarction [29]. Furthermore, it has been shown that TpTe value is high in Brugada syndrome patients with recurrent ventricular fibrillation and can be used to assess the risk of recurrent arrhythmia [17,30]. In the pediatric group with ADHD, there is only a single study on children receiving MPH monotherapy. In this study, electrocardiography results of children with ADHD on MPH before and two hours after drug intake are compared. The results indicate no significant difference between QTc, QTd, TpTe values while a statistically significant increase was observed in TpTe/QTc values [15]. In our study, the TpTe, TpTe dispersion and TpTe/QT ratio in the medically treated groups were significantly higher than those in the control group and untreated ADHD group. Furthermore, TpTe and TpTe/QT ratio was observed to be higher in the combination therapy group compared to the monotherapy groups. TpTe and TpTe/QT ratio was also significantly higher in the RIS group compared to the MPH group. The main limitation in the study conducted by Lamberti et al. was the lack of long term follow-up of patients since a 2-h period may not be sufficient to assess the effects of the drug on ECG results. In our study, on the other hand, the patients had been receiving regular treatment for a minimum of 3 months. Moreover, considering significantly highest ECG values in combination group due to these drugs created a stronger impact on the T wave when used together and RIS can possibly be responsible for this effect.

Combination therapies of psychostimulants and antipsychotics appear to be the most common treatment regime. The efficacy of both psychostimulants and antipsychotics for the treatment of ADHD and disruptive behavior disorders are supported by a reasonable amount of evidence. While combination therapy is recommended by several guidelines, concerns about the adverse effects related to the use of RIS and MPH together are increasing. Although cardiovascular effects of RIS and MPH combination therapy in the adult patient group has been investigated in quite a few studies, there is still insufficient research in the safety of this combination in pediatric patients. Thus, there is a need for further research assessing the effects of MPH and RIS combination therapy on ECG parameters in a large pediatric population with ADHD presenting high level of co-morbidity and requiring frequent combination therapy.

In this study, the number of RIS patients and patients on combination therapy was lower than the number of patients in other groups. Although the patients had no basal ECG before medication, untreated ADHD patient group was added to our study. On the other hand, patients who were on regular treatment for a minimum of 3 months also provided sufficient duration for the evaluation of drug effects. Besides, providing some information on the cardiovascular side effects of the drugs and evaluations of TpTe parameters of ADHD which presents high levels of co-morbidity and often requires combination therapy was another strength of the study.

Conclusion

There is a possible increased risk of sudden cardiac death in children with ADHD due to low levels of parasympathetic activity independent from other risk factors. The efficiency of MPH and RIS therapy, offering relative cardiac safety, has been proved in the treatment of ADHD, although these drugs may further elevate the risk of sudden cardiac death by increasing the ventricular repolarization. Thus, in this patient group, treatment indications must be identified more carefully and followed up with ECG parameters in pretreatment and during the treatment periods. Especially, children with prolonged QT on baseline ECG or family history of sudden death must be followed-up particularly. Besides, more useful predictors for evaluating the risk of arrhythmia including parameters such as TpTe, TpTe dispersion and TpTe/QT ratio in addition to basic ECG assessment in pediatric patients with ADHD would be beneficial.

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