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Blood pressure and heart rate in aripiprazole once – monthly and paliperidone 1 and 3-month long-acting preparations

Gokce Elif SARIDOGAN, Mehmet Zafer GOREN

Department of Pharmacology, School of Medicine, Marmara University, Istanbul, Turkey

Corresponding Author: Gokce Elif SARIDOGAN
E-mail: drgokcesaridogan@gmail.com

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ABSTRACT

Objective: This study aims to evaluate the blood pressure and heart rates of the patients treated with aripiprazole once-monthly, paliperidone 1-month, and paliperidone 3-month long-acting injections.

Patients and Methods: This study was a non-invasive observational study. Subjects using the same long-acting injection preparation for at least four months without skipped injections were assigned to 3 groups according to their treatments. They were screened starting from routine injection day and monthly for four months. Heart rate, systolic blood pressure, and diastolic blood pressure were recorded for each subject.

Results: Systolic and diastolic blood pressure among the three treatment groups demonstrated no statistical significance. The heart rate of the paliperidone 3-month group was significantly higher than the aripiprazole once-monthly group. However, the mean heart rate was within the physiological limits. Thus, a clinical significance can hardly be attributed.

Conclusion: Aripiprazole once-monthly, paliperidone 1-month, and paliperidone 3-month long-acting injections are non-inferior regarding heart rate, systolic and diastolic blood pressure during the maintenance treatment.

Keywords: Long-acting antipsychotic, Hypertension tachycardia, Schizophrenia, Maintenance treatment

1. INTRODUCTION

Schizophrenia is a mental disorder with various manifestations, with a mean worldwide prevalence of 0.5% [1]. Second-generation antipsychotics are the mainstream of the treatment, as well as long-acting injections (LAI) of these medications. Long-term maintenance and relapses are tremendously affected by the discontinuation of the antipsychotics, thus emphasizing the importance of adherence throughout the illness. Paliperidone palmitate is one of the recent LAIs shown to be effective and safe in schizophrenia treatment [2]. Another widely used newer LAI, Aripiprazole Once-Monthly (AOM), is the first LAI to be a D_2 partial agonist. Since the obstacle of non-adherence to oral antipsychotics exert a severe issue during the treatment, LAIs decrease the rates of hospitalizations, relapses, and overall cost of the illness [3,4].

Aripiprazole Once-Monthly has been previously reported to be non-inferior compared to placebo [5] and its oral form [6]. It exerts its effects through a partial agonism on D2 and 5-HT_{1A} receptors and antagonism on 5-HT_{2A} receptors [7]. The partial agonism of AOM provides a distinct action on positive and negative symptoms. On the other hand, histaminergic and α-adrenergic affinity without cholinergic activity leads to favorable tolerability [8].

Paliperidone is the active metabolite of risperidone. Paliperidone acts as an antagonist at D2, 5HT2A, α1, α2 adrenergic, and H1 histaminergic receptors with no affinity to muscarinic or β1 – and β2 receptors. Its receptor profile allows the agent to alleviate the positive symptoms with less tendency to induce extrapyramidal symptoms than typical antipsychotics [9].

Relapse rates of different formulations are documented. The lowest relapse rates were observed in Paliperidone 1-Month (P1M), Paliperidone 3-Month (P3M), and oral paliperidone, respectively. Furthermore, P3M, which can provide longer extended sustained release capacity with its larger particle size, was demonstrated to be as effective and safe as P1M [10,11].

Compared to P1M, AOM was reported to be superior in life quality, especially under 35-year-old patients, reflecting the

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interaction of both effectivity and safety parameters [12]. However, as the studies mentioned above mainly constitute findings from randomized controlled trials (RCTs), they can not objectively represent clinical, real-world practice due to artificial settings [13].

A limited number of studies reported a direct evaluation of blood pressure and heart rate related parameters, even though there is growing evidence from the case reports that aripiprazole and paliperidone can have clinical effects on these vital parameters. To our knowledge, AOM, P1M and P3M have not been previously compared for efficacy or tolerability related measures or in the maintenance treatment. Thus in this study, we assessed the monthly screening data for four months in order to evaluate the systolic blood pressure (SBP) and diastolic blood pressure (DBP), and heart rate (HR) values and their comparative analysis outcomes.

2. PATIENTS and METHODS

This study is designed and carried out as an observational, noninterventional naturalistic study. Clinical Studies Ethics Committee approved the study protocol and amendments (09.2019.468, date:03.05.2019) accordingly with the clinical approval of from the hospital and the local health authorities. The study was carried out in compliance with the Declaration of Helsinki and Good Clinical Practices. Volunteers among the patients and next to kin were informed about the research study and possible adverse reactions. Informed consent was obtained from all subjects after detailed information was provided.

During the maintenance treatment, patients who continued their treatments in the mental health center and the patients who were using AOM, P1M, and P3M preparations for the treatment of schizophrenia for at least four months before the study were included in this study and they were assigned to 3 groups according to their treatments. Adult patients aged between 18 and 65 were included in this study. Patients already being treated with one of the LAIs without a skipped dose and were treated only with monotherapy for at least four months participated in this study. Patients were previously diagnosed and met the criteria of diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, DSM-V).

Exclusion criteria included patients who lack a capacity of judgment or literacy in order to understand the study and the written consent, patients with dementia, significant suicide risk or behavior, substance dependence history within the last year, history of tardive dyskinesia or neuroleptic malign neuroleptic syndrome, involuntary hospitalization during screening, morbid obesity (BMI >40 kg/m2) and severe systemic disease that can be a contraindication for antipsychotic treatment.

Only short acting benzodiazepines, zopiclone, antiparkinsonian treatments, and all kinds of psychotherapy and psychosocial interventions were allowed during the study.

A sociodemographic data form was given to patients at day 0. The first observation was made right before their routine injection days. Screening days were determined as day 0, day 30, day 60, and day 90. On each screening day, SBP, DBP, and HR were recorded. SBP and DBP were recorded for four months monthly for each patient being present in the screening visit. SBP and DBP were recorded upon an independent investegator's (a trained health care professional) measuring blood pressure of the patients with a standard calibrated sphygmomanometer after they were at a seated position and relaxing on a chair for 10 min with a bare and stretched out upper arm supported and placed approximately at the heart level.

Patients were informed to avoid exposure to physical exertion, stress and caffeine intake at the day of the measurement. If they had significant pain or anxiety or if they were exposed to extreme heat or cold conditions this measurements were not taken into consideration in this study. At the same time heart rates of the patients were measured using a standard pulse oxymeter. All data were calculated as seperate monthly measures.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences software version 23.0 for Windows (SPSS Inc., Chicago, IL, USA).

Mean and standard deviation or standard error of the mean, number, and percentage values are given while assessing the categorical variables. The sample distribution was evaluated through histogram, qq plots, Shapiro Wilk, and Kolmogorov Smirnoff tests. Chi-Square test statistics and Fisher Exact Test were applied to assess the relationship between categorical variables.

The One Way ANOVA (One Way ANOVA) test statistic was used to compare the means of more than two groups. Bonferonni statistics were applied as a Post Hoc test in case of a significance with ANOVA. If the sample did not demonstrate a normal distribution, the Kruskal-Wallis test was used to compare more than two groups. If a significant difference was found between the groups, Bonferonni correction of the Mann-Whitney U test was applied for each group. The statistical significance was considered as <0.05.

3. RESULTS

In this study, the number of participants in the AOM, P1M, and P3M groups was 8, 9, and 8, respectively.

According to the treatment groups, there were 6 (75%) male subjects in the A1M group, and there were 7 (78%) in the P1M group and 4 (50%) in the P3M group. The number of female subjects in the A1M, P1M and P3M groups was 2 (25%), 2 (22.2%), and 4 (50%), respectively. Statistical significance was observed between the P1M and P3M groups ($\chi 2 = 0.251$, $p < 0.05$). There were no other significant differences among the sociodemographic measures in this study.

Blood pressure and heart rate measurements according to treatment groups are shown in Table 1.

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Table 1. *Blood Pressure and Heart Rate Measurements According to Treatment Groups*

	AOM (N=28) M ± SEM MRI	P1M (N=35) M ± SEM MRI	P3M (N=26) M ± SEM MRI	Total	F Value/ H Value	P value
Systolic Blood Pressure (mmHg)	109.29 ± 1.62 (28)	111.71 ± 1.5 (35)	113.52 ± 2.26(27)	111.5 ± 1.03(90)	3.058H	0.22
Mean Rank	39.64	45.69	51.33			
Diastolic Blood Pressure (mmHg)	71.07 ± 0.94 (28)	72 ± 0.8 (35)	73.33 ± 1.31 (27)	72.11 ± 0.58 (90)	2.171H	0.34
Mean Rank	41.61	45.14	50			
Heart rate (bpm)	81.64 ± 1.7 *(28)	90.37 ±1.88 **(35)	95.07±3.07 b (26)	89 ±1.39 (89)	8.727	0.0001***

*AOM: Aripiprazole Once-Monthly Long Acting Injection Form, P1M: Paliperidone 1-Month Long-Acting Injection Form, P3M: Paliperidone 3-Month Long-Acting Injection Form, M:Mean, SEM: Standard Error of Mean, MR:Mean Rank, N: Number of Measurements, * Statistically significant at the p <0.05 level. ** Statistically significant at p<0.01 level. *** Statistically significant at p<0.001 level. Different superscripts indicate that there is a statistical significance between groups.*

4. DISCUSSION

Most antipsychotics are well-documented to cause orthostatic hypotension, which is possibly related to α1-receptor antagonism action, peripheral vasodilation, and reflex tachycardia [14]. In addition to α1-receptor antagonism, some antipsychotics exert significant effects on histamine 1 receptors, such as olanzapine or clozapine, which may frequently lead to acute hypotensive states [15].

Besides, changes in long-term resting blood pressure and fluctuations due to antipsychotics are not well documented in the literature. However, existing reports indicate considerable evidence for hypertension and hypotension [16].

Another study to monitor the pulse, SBP, and DBP weekly for 6 weeks comparing paliperidone and olanzapine reported that the only significant statistical difference was observed with the DBP in the olanzapine group (p=0.02). However, this finding was reported as clinically non-significant [17].

In a study by Parks et al., risperidone and olanzapine were reported to significantly increase the SBP (p=0.01), while clozapine decreased this parameter (OR = 18.02; CI, 3.42-29.49) during the first three days of the treatment. However, authors also reported in the same study in which they assessed antipsychotic (including olanzapine, haloperidol, risperidone, clozapine, quetiapine, and ziprasidone) effects among 60 patients, 30% (16 participants) of which were hypertensive before the onset of antipsychotic administration 17% of the patients continued to stay hypertensive. Only two remained to have sustained hypertension throughout the study period. At the same time, the hypertensive patients at the study onset demonstrated a decrease of 20mmHg and 12 mmHg in SBP and DBP, respectively, while an overall decline in all samples in DBP was 2mmHg and SBP was 4mmHg. Non-hypertensive patients at the onset demonstrated only a 3mmHg decrease in SBP but no change in DBP [18].

Another study by Garcia-Portilla et al. reported no significant change in HR, SBP, or DBP at the endpoint during a 52-week follow-up P3M study [19].

In a case report, a patient with autism was described as developing hypertension after starting treatment with aripiprazole, and the dechallenge test restored the high blood pressure to normal levels [20]. Authors suggested that aripiprazole might be causing hypertension through its potential vasoconstriction effect through 5-HT2A receptors or inhibition of microglial nitric oxide. [21]. Similarly, another case report demonstrated that hypertension in a patient was normalized after dechallenge and reappeared after the rechallenge. This case was reported to respond well to propranolol. Thus adrenergic hyperactivity was suggested as a possible mechanism by the authors [22].

Similarly, our study found no difference among any treatment groups regarding DBP and SBP. Due to controversial findings in the literature and the rise in blood pressure reported in several case studies, hypertensive patients were advised to be carefully monitored [23]. However our study results did not raise a concern regarding DBP, SBP and heart rate in our sample during the study period.

Another adverse reaction of antipsychotics may be observed as tachycardia. This occurs most possibly due to anticholinergic properties, sometimes related to orthostatic hypotension via α1-adrenoreceptor antagonism or a feature of secondary neuroleptic malign syndrome or myocarditis [24, 25].

There are increasing numbers of case reports for paliperidone and paliperidone palmitate leading to increased heart rate and related morbidity. One of the case reports described a patient who developed tachycardia with risperidone, and the adverse condition was aggravated by paliperidone palmitate injection [26].

This result might be related to the fact that risperidone and its metabolite paliperidone are documented to be associated with different tachycardia presentations, such as multifocal atrial tachycardia, sinus tachycardia, and QTc prolongation [27,28, 29]. Paliperidone was reported to be associated with tachycardia in 14% of the cases, which also may start the day after the administration of the agent [30,31].

On the other hand, aripiprazole was not accounted for cardiac risk factors in healthy subjects [32].

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Furthermore, QTc prolongation with aripiprazole is reported to be less significant than the conventional antipsychotics. [33]. However, a case report demonstrated that a 13-year-old girl with early-onset schizophrenia developed arrhythmia with aripiprazole [34]. In Another recent case report, tachycardia, headache, nausea, and high blood pressure was reported in a 53-year-old woman. Authors suggested a role for dopaminergic receptor interaction with the renin-angiotensin-aldosterone system [35].

In our study, HR was significantly higher in the P3M group compared with the AOM group. However, since the mean HR of the groups is within the physiological limits, this may not account for clinical significance.

The limitations of our study include our small sample size and statistical differences in the gender variable among P1M and P3M groups. Further studies are needed to address the SBP, DBP, and HR fluctuations to shed light on the controversial and limited data in the literature.

Conclusion

All three LAI preparations, AOM, P1M, and P3M, demonstrated a safe profile during four months with monthly assessments of blood pressure and heart rate in schizophrenia patients during the maintenance treatment. The heart rate was statistically significantly higher in P3M group compared to AOM however this difference was between physiological limits, thus a clinical significance was not noted. None of the paliperidone formulations were inferior to aripiprazole long acting formulation regarding vital signs. There was no significant difference among the 1 and 3 month sustained release formulations of paliperidone.

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Compliance with Ethical Standards

Ethical approval: Clinical Studies Ethics Committee approved the study protocol and amendments (09.2019.468, date: 03.05.2019) accordingly with the clinical approval of from the hospital and the local health authorities. The study was carried out in compliance with the Declaration of Helsinki and Good Clinical Practices. Informed consent was obtained from all subjects after detailed information was provided.

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