Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effects of four atypical antipsychotics on autonomic nervous system activity in schizophrenia

Saki Hattori [a,*], Ikuko Kishida [a,b], Akira Suda [a], Masatoshi Miyauchi [a], Yohko Shiraishi [a], Mami Fujibayashi [c], Natsuki Tsujita [d], Chie Ishii [b], Norio Ishii [b], Tosiho Moritani [e], Masataka Taguri [f], Yoshio Hirayasu [a]

[a] Department of Psychiatry, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan
[b] Fujisawa Hospital, 383 Kotuka Fujisawa, Kanagawa 251-8530, Japan
[c] Division of Physical and Health Education, Setsunan University, 17-8 Ikedanakamachi, Neyagawa, Osaka 572-8508, Japan
[d] Graduate School of Human and Environmental Studies, Kyoto University, Yoshidanihonmatsucho, Sakyo-ku, Kyoto 606-8316, Japan
[e] Faculty of General Education, Kyoto Sangyo University, Kamo-motoyama, Kita-ku, Kyoto 606-8555, Japan
[f] Department of Biostatistics, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan

ARTICLE INFO

Article history:
Received 14 April 2017
Received in revised form 27 June 2017
Accepted 2 July 2017
Available online xxxx

Keywords:
Schizophrenia
Atypical antipsychotic drug
Heart rate variability
Autonomic nervous system

ABSTRACT

Antipsychotic drugs are associated with autonomic nervous system (ANS) dysfunction in patients with schizophrenia, but the effects of individual atypical antipsychotic drugs are not clear. This study investigated how four atypical antipsychotic drugs—risperidone, olanzapine, aripiprazole, and quetiapine—differ in their effects on ANS activity. A total of 241 Japanese patients with schizophrenia participated in this study. All of the participants received an atypical antipsychotic as monotherapy: 90 participants received risperidone, 68 olanzapine, 52 aripiprazole, and 31 quetiapine. ANS activity was assessed by means of a power spectral analysis of heart rate variability. The quetiapine group showed significantly diminished sympathetic and parasympathetic activity compared with the risperidone and aripiprazole groups and significantly lower sympathetic activity relative to olanzapine. In addition, multiple regression analysis showed that the type of antipsychotic drug significantly influenced ANS activity. We suggest that, among the antipsychotics examined—risperidone, olanzapine, aripiprazole and quetiapine—quetiapine has the strongest effect on ANS activity.

1. Introduction

Patients with schizophrenia have a mortality risk that is two to three times that of the general population (Brown et al., 2010; Olfson et al., 2015; Walker et al., 2015), and one of the notable causes of death is cardiovascular disease (Brown et al., 2010; Healy et al., 2012; Ifteni et al., 2014; Koponen et al., 2008; Olfson et al., 2015). Antipsychotic medications have been linked to cardiovascular adverse effects and cases of unexplained sudden death (Appleby et al., 2000; Mentonen et al., 1991). However, the mechanisms underlying the increased risk are unknown, and the pathology of sudden death during antipsychotic drug treatment urgently needs clarification.

Previous studies have reported that antipsychotic medications can exacerbate autonomic nervous system (ANS) dysfunction in schizophrenic patients (Agelink et al., 2001; Birkhofer et al., 2013; Cohen et al., 2001; Huang et al., 2013; Ieda et al., 2014; Iwamoto et al., 2012; Kim et al., 2004), and decreased ANS activity is associated with morbidity and sudden death due to cardiovascular disease (Thayer et al., 2010). We have reported that antipsychotic drugs significantly decrease ANS activity in a dose-dependent manner (Iwamoto et al., 2012). However, the effects of individual antipsychotic drugs on the ANS have not been elucidated. Although olanzapine and other antipsychotic drugs have been compared (Hempel et al., 2009; Wang et al., 2008), sample sizes were small and the studies did not include atypical antipsychotic drugs whose use has increased in recent years. Each antipsychotic drug is likely to affect the ANS differently because each has a different affinity for various neurotransmitter receptors.

In this study, we investigated the separate effects on ANS activity of four atypical antipsychotic drugs: risperidone, olanzapine, quetiapine, and aripiprazole. A comparison of ANS activities associated with these representative atypical antipsychotics could provide clinicians with useful information about antipsychotic characteristics and safer use of atypical antipsychotics.

* Corresponding author.
E-mail addresses: saki1122@yokohama-cu.ac.jp (S. Hattori), kasuga@yokohama-cu.ac.jp (I. Kishida), sudaakira_ycu@yahoo.co.jp (A. Suda), miyauchi-masatoshi@hotmail.co.jp (M. Miyauchi), yohko.iwamoto@gmail.com (Y. Shiraishi), fujibayashi@atf.setsunan.ac.jp (M. Fujibayashi), natsuki.morita823@gmail.com (N. Tsujita), chie@fox.dti2.ne.jp (C. Ishii), ishiinorio@jcom.home.ne.jp (N. Ishii), moritani.toshio.76s@st.kyoto-u.ac.jp (T. Moritani), taguri@yokohama-cu.ac.jp (M. Taguri), hirayasu@yokohama-cu.ac.jp (Y. Hirayasu).

http://dx.doi.org/10.1016/j.schres.2017.07.004
0920-9964/

2. Methods

2.1. Participants

The study involved 241 Japanese patients with schizophrenia (57 inpatients and 184 outpatients; 99 men and 142 women; mean age ± standard deviation, 51.7 ± 15.7 years). The study used a cross-sectional design in a consecutive sample of patients with schizophrenia at Fujisawa Hospital and Yokohama City University Hospital in Japan from July 2007 to March 2017. We recruited patients with schizophrenia who received one of the atypical antipsychotic drugs risperidone, olanzapine, aripiprazole, and quetiapine as monotherapy for >3 months. None of the antipsychotics had been adjusted in the previous 3 months. We excluded participants who could not take the antipsychotics as prescribed and attend the hospital for at least 1 year. Patients were diagnosed by psychiatrists with sufficient clinical experience using criteria based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1994). Participants who had cardiovascular, respiratory, neurological, or endocrine illness, a current or past history of substance abuse that obscured diagnosis, or were taking medication for physical diseases were excluded.

To assess symptom severity, we used a Japanese translation of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Psychiatrists with sufficient clinical experience assessed patients' positive, negative, and general signs using the PANSS on the day on which electrocardiography (ECG) was recorded.

Clinical information on the participants was obtained from their medical records. We investigated all psychotropic medications given, including antipsychotic, antiparkinsonian, and benzodiazepine agents. The doses were calculated using conversions to standard equivalents of chlorpromazine, biperiden, and diazepam (Inada and Inagaki, 2015).

The study was performed in Fujisawa Hospital and Yokohama City University Hospital in Japan. The study protocol was approved by the ethics committee of Fujisawa Hospital, and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants after they received a full explanation of the study.

2.2. R-R interval power spectral analysis

We performed a computer-assisted measurement of 5-min resting heart rate variability (HRV) to noninvasively evaluate ANS activity, as in our previous studies (Fujibayashi et al., 2009; Kimura et al., 2006). HRV power spectral analysis is a noninvasive method that can be used to assess autonomic imbalance. The technique used in the present investigation to detect the three major spectral components of HRV has been previously applied under diverse psychophysiological conditions in basic medical science and clinical research. The validity, reliability, and practicability of this technique have been well documented (Matsumoto et al., 1999; Matsumoto et al., 2006; Moritani et al., 2005). All experimental sessions took place between 09:00 and 12:00. Participants did not consume caffeine or smoke from the morning on the measurement day. We performed the ECG with patients in a seated position for 5 min after resting for at least 10 min beforehand. HRV power spectral analysis decomposes a series of sequential R–R intervals obtained from the 5-min ECG into a sum of sinusoidal functions of different amplitudes and frequencies by fast Fourier transform (Akselrod et al., 1981; Fujibayashi et al., 2009; Kimura et al., 2006; Pagani et al., 1986; Pomeranz et al., 1985; Rompelman et al., 1977). Spectral power was quantified in the frequency domain by calculating the areas under the curve in the following frequency bands as in our previous studies (Fujibayashi et al., 2009; Kimura et al., 2006; Matsumoto et al., 1999; Matsumoto et al., 2006; Moritani et al., 2005): the low-frequency (LF; 0.03–0.15 Hz) HRV, indicating both sympathetic and parasympathetic nerve activity; high-frequency (HF; 0.15–0.40 Hz) HRV, indicating primarily parasympathetic nerve activity; and total power (TP; 0.03–0.40 Hz), indicating overall ANS activity (Akselrod et al., 1981; Pagani et al., 1986; Pomeranz et al., 1985).

2.3. Statistical analysis

All statistical analyses were carried out with SPSS for Windows version 24 (SPSS, Chicago, IL). One-way analyses of variance (ANOVA) were used to examine group differences in clinical characteristics (age, disease duration, body mass index [BMI], dose of antipsychotic drugs, dose of anticholinergics, dose of benzodiazepines, PANSS score) and the LF, HF, and TP components of HRV. The proportions of men and women, inpatients and outpatients, and smokers and non-smokers were examined using the chi-squared test. As a post hoc analysis, between-group estimated marginal means were compared with confidence interval adjustment using the Tukey test. In addition, the effect of clinical factors on ANS activity was assessed by multiple regression analysis. Dependent variables were the LF, HF, and TP components of the HRV; independent variables that could affect ANS activities were age, sex, BMI, disease duration, PANSS score, dose of anticholinergics, dose of benzodiazepines, and type of antipsychotic (Chang et al., 2013; Huang et al., 2013; Kim et al., 2011; Wang et al., 2014). We assessed the relationship between all of the components of HRV and the type of antipsychotic after adjusting for these possible factors. Due to skewed data, the absolute values of the HRV spectral components were log-transformed prior to statistical analysis. The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Comparison of the effects of risperidone, olanzapine, aripiprazole, and quetiapine on ANS

There were 90 participants in the risperidone group, 68 participants in the olanzapine group, 52 participants in the aripiprazole group, and 31 participants in the quetiapine group. The demographic and medication data of all participants are shown in Table 1. Except for age ($p < 0.001$) and disease duration ($p = 0.005$), there were no significant differences in demographics among the four groups. There were also no significant differences in the PANSS score or mean dose of the given antipsychotic drugs, anticholinergic drugs, or benzodiazepines among the groups.

As shown in Table 2, LF, HF, and TP differed significantly among the four groups (LF, $p = 0.001$; HF, $p = 0.007$; TP, $p = 0.001$). For all of the components of HRV, power values increased in the order of the quetiapine group, olanzapine group, risperidone group, and aripiprazole group. When we divided each group into two groups using a cutoff age of 47 years old to eliminate the effect of age, splitting the participants in the quetiapine group (the smallest group) into two even groups, LF, HF, and TP differed among the four groups, in line with the results for all participants (higher age group: LF, $p = 0.007$; HF, $p = 0.05$; TP, $p = 0.004$; younger age group: LF, $p = 0.032$; HF, $p = 0.089$; TP, $p = 0.055$).

As shown in Fig. 1, a post hoc analysis revealed that LF was significantly lower in the quetiapine group than in the risperidone group ($p = 0.004$) and aripiprazole group ($p = 0.001$). Similarly, HF was significantly lower in the quetiapine group than in the risperidone group ($p = 0.035$) and aripiprazole group ($p = 0.004$) as shown in Fig. 2. TP was significantly lower in the quetiapine group than in the risperidone group ($p = 0.003$) and aripiprazole group ($p = 0.001$), but lower than in the olanzapine group ($p = 0.047$) as shown in Fig. 3.

3.2. Association between ANS activity, antipsychotics, and other factors

Table 3 shows the results of multiple regression analysis. All of the HRV components were significantly associated with age and type of antipsychotic drug. In addition, the LF and TP components of HRV were

Please cite this article as: Hattori, S., et al., Effects of four atypical antipsychotics on autonomic nervous system activity in schizophrenia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.004