ORIGINAL RESEARCH

Effects of long-acting injectable antipsychotics versus oral antipsychotics on autonomic nervous system activity in schizophrenic patients

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Objective: Long-acting injections (LAIs) of antipsychotics show distinct pharmacokinetic profiles from oral antipsychotics (OAPs). Although there may be differences in adverse event frequency, any differences in their effects on autonomic nervous system (ANS) remain unclear.

Patients and methods: In total, 270 schizophrenic patients were recruited in this study: 241 received OAPs (risperidone, olanzapine, quetiapine, or aripiprazole) and 29 received LAIs (risperidone LAI, aripiprazole LAI, or paliperidone palmitate) as monotherapy. Heart rate variability was measured as an index of ANS activity, and the low-frequency (0.03–0.15 Hz) component, high-frequency (0.15–0.40 Hz) component, and total power (0.03–0.40 Hz) were calculated. Components were compared between the groups using t-tests.

Results: A significant difference was detected in the low-frequency component between the OAP and LAI groups ($P=0.046$). No significant difference was found in total power or the high-frequency component between the two groups.

Conclusion: Compared with OAPs, LAIs have fewer adverse effects on ANS activity, particularly the low-frequency component, as determined using a spectral analysis of heart rate variability.

Keywords: long-acting injectable antipsychotics, autonomic nervous system, heart rate variability, adverse effect

Introduction

The mortality risk of schizophrenic patients is two to three times higher than that of the general population,[1–3] and one of the notable causes of death is cardiovascular disease.[1,2,4–6] Some explanations have been advanced for the higher risk of cardiovascular disease in these patients. For example, antipsychotic medication has been linked to cardiovascular adverse effects and unexplained sudden death.[7,8] However, why sudden death can occur during treatment with antipsychotics remains unclear.

In schizophrenic patients, antipsychotics are strongly associated with dysfunction of the autonomic nervous system (ANS),[9–15] and decreased ANS activity is associated with morbidity and sudden death due to cardiovascular disease.[16] We previously reported the dose-dependent adverse effects of antipsychotic drugs on ANS activity and suggested that higher blood levels of antipsychotics decrease ANS activity.[14]

Long-acting injections (LAIs) of antipsychotics are an important option for relapse prevention, especially for nonadherent patients.[17–21] In terms of safety and tolerability, meta-analysis results suggest that LAIs and oral antipsychotics (OAPs) do not differ with respect to the frequency of treatment discontinuation due to adverse events.[22,23] However, it is important to note that LAIs have different pharmacokinetic profiles

from OAPs, which could be associated with fewer adverse events. Taipale et al reported that LAI use is associated with an ~30% lower risk of death compared with oral agents.[24] Another study reported that extrapyramidal symptoms were possibly improved in patients treated with LAIs.[25] A recent study also indicated that switching from oral risperidone to LAI improved verbal capability.[26] Some other studies suggest that serum prolactin levels are lower with LAIs than with OAPs.[27–29] Therefore, LAIs could have fewer ANS activity-related adverse effects compared with OAPs. However, as far as we know, no previous studies have compared LAIs and OAPs in the presymptomatic state.

Therefore, in this study, we investigated the effects of four atypical antipsychotic drugs and three LAIs of atypical antipsychotics on ANS activity. We evaluated ANS activity noninvasively by assessing 5-minute resting heart rate variability (HRV), which can indicate autonomic imbalance. HRV power spectral analysis has been used in both basic medical science and clinical research to identify the three major spectral components of HRV under various psychophysiological conditions, and its reliability, validity, and practicability are well documented.[30–32] Comparing ANS activities associated with the two groups could offer important information on antipsychotic safety.

Patients and methods
Participants
This cross-sectional study assessed 270 consecutive Japanese schizophrenic patients (62 inpatients and 208 outpatients; 142 women; mean age±SD, 51.68±15.65 years) receiving treatment at Fujisawa Hospital and Yokohama City University Hospital, Japan, from July 2007 to November 2017. All patients had received either an OAP (risperidone, olanzapine, aripiprazole, or quetiapine) or an LAI (risperidone LAI, aripiprazole LAI, or paliperidone palmitate) as monotherapy for >3 months at the same dosage and without adjustment in the previous 3 months. The 241 patients in the OAP group were those involved in our previous study comparing the effects of the same four OAPs on ANS activity,[33] and the patients receiving LAI were newly recruited for the present study. In the LAI group, 17 patients (58.6%) received paliperidone palmitate, 9 (31.0%) received aripiprazole LAI, and 3 (10.3%) received risperidone LAI.

All participants were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition[34] by sufficiently experienced psychiatrists. Patients unable to take the antipsychotics as prescribed and/or attend the hospital for at least 1 year were excluded, as well as those with current or past history of substance abuse possibly obscuring diagnosis or any neurological, endocrine, respiratory, or cardiovascular illness. Also excluded were any patients receiving medication for physical conditions. Severity of patients' positive, negative, and general signs was assessed using a Japanese translation of the Positive and Negative Syndrome Scale (PANSS)[35] on the day the electrocardiography (ECG) was recorded. Participants' clinical information was collected from their medical records. All prescribed psychotropic medications were assessed, including antiparkinsonian, antipsychotic, and benzodiazepine agents. Doses were calculated by conversion to standard equivalents of biperiden, chlorpromazine, and diazepam.[36]

The protocol was approved by the institutional ethics committee of Fujisawa Hospital and adhered to the Declaration of Helsinki. Participants provided written informed consent after receiving a complete explanation of the study.

R–R interval power spectral analysis
As in our previous studies,[38,39] 5-minute resting HRV was assessed to evaluate ANS activity noninvasively. All measurements were performed between 09:00 and 12:00. The ECG was performed for 5 minutes in seated patients who had not consumed caffeine or smoked that morning and had rested for at least 10 minutes beforehand. In HRV power spectral analysis, a series of sequential R–R intervals obtained from the 5-minute ECG are decomposed via fast Fourier transform into the sum of sinusoidal functions of different amplitudes and frequencies.[37–42]

As in our previous studies,[30–32,37,38] the areas under the curve in the following frequency bands were determined to quantify the spectral power in each frequency domain: low-frequency (LF; 0.03–0.15 Hz) HRV, high-frequency (HF; 0.15–0.40 Hz) HRV, and total power (TP; 0.03–0.40 Hz).[39–41] These domains correlate to sympathetic and parasympathetic nerve activity, primarily parasympathetic nerve activity, and overall ANS activity, respectively.

Statistical analysis
Student's *t*-tests were used to assess differences in clinical characteristics (age, body mass index [BMI], disease duration, antipsychotic drug dose, anticholinergic agent dose, benzodiazepine agent dose, and PANSS score) and the LF, HF, and TP components of HRV. The chi-squared test was used to examine the proportions of male and female participants, inpatients and outpatients, and smokers and non-smokers. The effects of clinical factors on ANS activity were evaluated using multiple regression analysis. The LF,

HF, and TP components of the HRV were considered as the dependent variables, whereas the independent variables possibly affecting ANS activity were age, BMI, PANSS score, and antipsychotic drug formulation.[12,43] After adjustment for these possible factors, the relationship between all HRV components and the drug formulation was assessed. Because the data were skewed, the absolute values of the HRV spectral components were log-transformed before the statistical analysis. The statistical analysis was performed using SPSS for Windows version 24 (IBM Corporation, Armonk, NY, USA). A P-value <0.05 was considered significant.

Results

The demographic and medication data of the 241 participants in the OAP group and the 29 participants in the LAI group are shown in Table 1. There were no significant differences in demographics, PANSS score, anticholinergics, or benzodiazepines between the two groups. However, the mean dose of antipsychotics administered was significantly higher in the LAI group (P=0.021).

As shown in Table 2, there was a significant difference in the LF component between the OAP and LAI groups (P=0.001), but no significant difference in TP or the HF component.

Multiple regression analysis revealed that all three HRV components were significantly associated with age. Because the strong association of age with HRV had already been

Table 1 Participants' demographic and medication data

	Oral drug (n=241)	LAI (n=29)	P-value
Age (years)	51.68±15.65	46.90±11.94	0.056
Sex (male/female)	99/142	8/21	0.160
Inpatient/outpatient	57/184	5/24	0.438
Duration of illness (years)	20.13±14.71	14.71±11.40	0.143
Smoking (smoker/non-smoker)	20/221	1/28	0.357
BMI (kg/m²)	24.15±4.46	24.16±5.25	0.989
CPZeq[b] (mg/day)	459.23±232.88	564.0345±197.63	0.021[a]
BPDeq[c] (mg/day)	0.82±1.54	1.21±2.11	0.227
DZPeq[d] (mg/day)	5.92±8.76	8.15±11.62	0.214
PANSS total score	71.69±15.25	72.69±16.89	0.743

Notes: Data are presented as mean±SD. Age, duration of illness, BMI, CPZeq, BPDeq, DZPeq, and PANSS total score were compared between the groups using t-tests. The proportions of men/women, inpatients/outpatients, and smokers/non-smokers were compared between the groups using a chi-squared test. [a]Significant difference (P<0.05; t-test). [b]Daily dose of antipsychotic drugs was converted to an approximate chlorpromazine equivalent. [c]Daily dose of anticholinergic antiparkinsonian drugs was converted to an approximate biperiden equivalent. [d]Daily dose of benzodiazepine was converted to an approximate diazepam equivalent.
Abbreviations: BMI, body mass index; BPDeq, biperiden equivalent; CPZeq, chlorpromazine equivalent; DZPeq, diazepam equivalent; LAI, long-acting injection; PANSS, Positive and Negative Syndrome Scale.

Table 2 Log-transformed power values of the LF, HF, and TP frequency bands compared between the oral drug group and the LAI group

	Oral drug (n=241)	LAI (n=29)	P-value
lnLF (ms²)	4.30±1.26	4.79±1.07	0.048[a]
lnHF (ms²)	3.83±1.46	4.01±1.10	0.532
lnTP (ms²)	4.92±1.25	5.25±1.00	0.171

Notes: Data are presented as mean±SD. [a]Significant difference (P<0.05).
Abbreviations: HF, high frequency; LAI, long-acting injection; LF, low frequency; ln, natural log-transformed; TP, total power.

reported,[43,44] we performed multiple regression analyses excluding age. Consequently, the antipsychotic formulation was significantly associated with the LF component (Table 3), but not with the HF component or TP. There were no associations between any of the components of HRV and the PANSS score or BMI.

Discussion

This study is the first to analyze the different effects of OAPs and LAIs on ANS activity, which were assessed using the noninvasive method of HRV power spectral analysis. Our results reveal significant differences in HRV between OAP and LAI patients. The LF component values were lower in the OAP group, even though their mean dose of given antipsychotics was lower. Because the LF component represents sympathetic and partially vagal modulation, our results suggest that the sympathetic nervous activity is lower in OAP patients.

Bioequivalence to oral formulations has been established for LAIs. On the other hand, some previous studies suggest that LAIs have better safety and tolerability than OAPs. Some suggest that serum prolactin levels are lower with LAIs than with OAPs.[27–29] Some also suggest that switching from paliperidone to paliperidone palmitate decreases extrapyramidal side effect liability.[29,45] The steady-state, peak-to-trough, plasma concentration ratios of risperidone vary according to the type of drug, with the results indicating that LAIs have lower peak-to-trough blood level variations than OAPs.[46,47] We previously reported that antipsychotic medications can exacerbate ANS dysfunction in schizophrenic patients in a dose-related fashion.[14] Considering that many previous studies support a significant correlation between plasma concentration and increased adverse events,[48,49] this pharmacokinetic difference between the two preparations could be associated with the frequency of adverse effects of LAIs. Therefore, this pharmacokinetic profile could help to explain our results.

Table 3 Results of multiple regression analysis with ANS activity, BMI, PANSS total score, and type of antipsychotic drug as independent variables

Independent variables	ANS activity					
	lnLF		lnHF		lnTP	
	B	**P-value**	**B**	**P-value**	**B**	**P-value**
BMI (kg/m²)	−0.075	0.218	−0.062	0.314	−0.081	0.185
PANSS, total score	−0.018	0.771	−0.094	0.126	−0.044	0.470
Drug formulation (oral/LAI)	0.121	0.047[a]	0.040	0.511	0.085	0.166

Note: [a]Significant difference ($P<0.05$; multiple regression analysis).
Abbreviations: ANS, autonomic nervous system; BMI, body mass index; HF, high frequency; LAI, long-acting injection; LF, low frequency; ln, natural log-transformed; PANSS, Positive and Negative Syndrome Scale; TP, total power.

A recent report showed no significant differences between LAIs and OAPs in terms of cardiovascular adverse events.[23] In our study, we excluded individuals with any diagnosed cardiovascular complication to estimate their ANS activity at a presymptomatic state. We need to investigate the course of the two groups over a longer period of time to clarify whether the lower effect of the drugs on ANS activity could lead to lower risks of cardiovascular events.

Multiple regression analysis revealed significant associations between the drug formulations of the atypical antipsychotic drugs and all components of ANS activity. However, BMI and the PANSS score were not associated with any component of ANS activity, suggesting that formulations of atypical antipsychotics alone affect the LF component. Also, our results showed that drug formulations are unlikely to be influenced by the HF component and TP. The HF component of HRV is also reported to have a stronger association with various factors, including the severity of negative symptoms, compared with the LF component.[50–52] Thus, the effect of severity might lessen the influence of the drug formulation on the HF component.

This study has some limitations. First, the number of participants was small, especially in the LAI group, and we could not perform subanalysis to compare OAPs and LAIs of the same drug. Second, we could not elucidate causal relationships due to the cross-sectional design. Third, various factors such as treatment history may have caused variation in the ANS activities before the patients were grouped. Fourth, we could not eliminate the effect of difference in antipsychotic doses between the two groups. In addition, because of the age differences between the study groups, we could not exclude the possibility that age affects ANS activity or interacts with the effects of antipsychotics.

Conclusion

As determined using HRV power spectral analysis, LAIs have fewer adverse effects on ANS, particularly sympathetic nerve activity, than OAPs. We need to clarify the course of patients with decreased ANS activity and perform further studies with larger populations to clarify the safety of LAIs in terms of ANS activity.

Disclosure

The authors report no conflicts of interest in this work.

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