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Differences in plasma prolactin levels in patients with schizophrenia treated on monotherapy with five second-generation antipsychotics

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ABSTRACT

Although second-generation antipsychotics (SGAs) are characterized by fewer prolactin (PRL)-related side effects compared with first-generation antipsychotics, the detailed effects of SGAs on the plasma PRL levels still remain unclear. We examined the differences in plasma PRL levels among 268 patients treated for schizophrenia with olanzapine (OLZ), risperidone (RIS), aripiprazole (ARP), quetiapine (QTP), or perospirone (PER). The participants had received antipsychotic monotherapy with stable doses of OLZ, RIS, ARP, QTP, or PER for ≥3 weeks, and fasting blood samples were drawn to examine plasma PRL levels. The differences in median plasma PRL levels in all ($P<0.001$), male ($P<0.001$) and female patients ($P<0.001$) among the five SGA groups were statistically significant. A stepwise multiple regression analysis showed that ARP treatment was found to contribute to lower plasma PRL level, while female sex, RIS, OLZ and chlorpromazine equivalent dose were found to contribute to a higher plasma PRL level. The median value of plasma PRL level in the RIS group was twice as much compared with that in the OLZ group, although this was not statistically significant. In this study, OLZ had a considerable effect on plasma PRL level, similar to RIS, while PER did not affect plasma PRL levels, similar to QTP. Further studies are needed to clarify the differences in plasma PRL levels among SGAs.

1. Introduction

Hyperprolactinemia, an adverse effect of first-generation antipsychotics and some second-generation antipsychotics (SGAs), can cause sexual dysfunction and galactorrhea. In the long term, hyperprolactinemia is associated with decreased bone density, which leads to osteoporosis (Dickson and Glazer, 1999). SGAs are characterized by fewer prolactin (PRL)-related side effects compared with first-generation antipsychotics owing to their mild dopaminergic blockade activity (Madhusoodanan et al., 2010). Risperidone (RIS) causes more marked elevations in plasma PRL levels than do other SGAs (Kleinberg et al., 1999; Lieberman et al., 2005; Madhusoodanan et al., 2010). On the other hand, olanzapine (OLZ) has less of an effect on the concentration of PRL than does RIS (Lieberman et al., 2005; Fraguas et al., 2011). We previously reported that OLZ induces elevation of PRL in a dose-dependent manner (Suzuki et al., 2011); therefore, the effect of high doses of OLZ on plasma PRL levels should be investigated to clarify the difference in the effects on plasma PRL levels of RIS and OLZ treatments.

Quetiapine (QTP) has a lower affinity for dopamine D2 receptors than other SGAs and shows a transient dopamine D2 occupancy; it is predicted that these properties underlie the negligible effect of QTP on plasma PRL level (Kapur et al., 2000). Nevertheless, there have been few studies directly comparing difference in plasma PRL levels between QTP and other SGA treatments.

Perospirone (PER), cis-N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl] cyclohexane-1,2-dicarboximide monohydrochloride, is a novel antipsychotic agent developed in Japan that is used for the treatment of schizophrenia and related illnesses. PER has both dopamine D2 antagonist and serotonin 5-HT2 antagonist effects (Hirose et al., 1990). PER affects not only the positive symptoms, but also the negative symptoms of schizophrenia (Onrust and McClellan, 2001; de Paulis, 2002). However, the effects of PER on plasma PRL levels remain unclear.

In the present study, we examined differences in plasma PRL levels among patients treated with either OLZ, RIS, QTP, PER or aripiprazole (ARP).

2. Methods

2.1. Participants

The study was conducted in 268 inpatients or outpatients aged 17–65 years. Table 1 shows the clinical characteristics of the participants. Each participant's condition had to be stable for inclusion in the study (i.e., no significant improvement or worsening of symptoms within the past 2 months). The participants had received stable doses

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Table 1
Sample description.

Variables	
Mean ± SD age (years)	34.5 ± 12.0
Male/female (n)	133/135
Inpatient/outpatient (n)	196/72
Mean ± SD body mass index (kg/m2)	22.2 ± 4.5
BPRS	28.1 ± 10.0
Breakdown of antipsychotics (n)	
Olanzapine	72
Risperidone	70
Aripiprazole	67
Quetiapine	33
Perospirone	26

Abbreviations: SD = standard deviation.
BPRS = Brief Psychiatric Rating Scale.

of OLZ, RIS, ARP, QTP, or PER for ≥3 weeks for the treatment of schizophrenia. We excluded participants with the following conditions: an overt physical illness, changes in drug therapy within the previous 2 weeks, concurrent treatment with other antipsychotic agents, or concurrent treatment with any drugs other than benzodiazepines. The Brief Psychiatric Rating Scale was used to evaluate the psychotic symptoms of participants. This study was conducted with the approval of the Gene Ethics Committee of Niigata University Graduate School of Medical and Dental Sciences. All participants were provided thorough explanations of the study prior to giving their written informed consent.

2.2. Methods for evaluation and determination of plasma PRL level

Fasting blood samples were drawn to examine plasma PRL levels at 7:00 a.m. Plasma PRL levels were assayed by an enzyme immunoassay. The body mass index (BMI; weight in kilograms divided by the square of the height in meters) was calculated.

2.3. Statistical analysis

Differences among the five SGA groups in terms of chlorpromazine (CP) equivalent dose, age, sex distribution and BMI were tested by one-way analysis of variance or the chi-square test. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess whether the data were normally distributed. Because the plasma PRL levels were not normally distributed, differences in plasma PRL levels among the five SGA groups were evaluated by a non-parametric Kruskal–Wallis test. A logarithmic transformation was subsequently applied to the plasma PRL levels to perform a multiple regression analysis. A stepwise multiple regression analysis was conducted to evaluate the effects of various independent variables, including CP equivalent dose, age, sex, BMI, and the type of SGA (OLZ, RIS, ARP, QTP, and PER) on plasma PRL levels. The threshold for significance was set at $P<0.05$. SPSS-19.0 (IBM Japan Ltd., Tokyo, Japan) software was used to perform statistical analyses.

3. Results

3.1. Differences in plasma PRL levels among the five SGA groups

Table 2 shows the characteristics of the five SGA groups. There were no significant differences in age, sex distribution and BMI among the five SGA groups. The difference in CP equivalent dose among the five SGA groups was statistically significant ($df=4$, $F=26.171$, $P<0.001$). Post-hoc analyses showed that the mean CP equivalent doses in the OLZ and QTP groups were statistically and significantly higher than those in the RIS ($P<0.001$), ARP ($P<0.001$), and PER groups ($P<0.001$).

The differences in median plasma PRL levels in all ($P<0.001$), male ($P<0.001$) and female patients ($P<0.001$) among the five SGA groups were statistically significant. Post-hoc analyses showed that the median PRL level in the RIS group was significantly higher than that in the ARP ($P<0.001$), QTP ($P<0.001$) and PER groups ($P<0.001$), and that the median plasma PRL level in the OLZ group was significantly higher than that in the ARP ($P<0.001$), QTP ($P=0.021$) and PER groups ($P<0.001$). The median plasma PRL level in the ARP group was significantly lower than that in the QTP group ($P<0.001$).

3.2. Stepwise multiple regression analysis of the effects of SGA on plasma PRL levels

We conducted a stepwise multiple regression analysis to evaluate the effects of various independent variables, including CP equivalent dose, age, sex, BMI, and the type of SGA (OLZ, RIS, ARP, QTP, and PER) on the natural logarithm of the plasma PRL levels (Table 3). We analyzed the type of SGA, sex and CP equivalent dose and found them to be significantly associated with the natural logarithm of the plasma PRL levels. ARP was found to contribute to lower plasma PRL levels, while female sex, RIS, OLZ and CP equivalent dose were found to contribute to a higher plasma PRL level.

4. Discussion

The results of this study suggest that ARP treatment decreases plasma PRL levels and that RIS and OLZ treatments increase plasma PRL levels, compared with QTP and PER treatments, which had little effect on plasma PRL levels. To the best of our knowledge, this is the first study to directly demonstrate differences in the effects of five SGAs, including ARP and PER, on the plasma PRL level. RIS causes more marked elevations in plasma PRL level than do other SGAs (Kleinberg et al., 1999; Lieberman et al., 2005; Fraguas et al., 2011). A double-blind randomized trial revealed a moderate increase in plasma PRL level with OLZ, an intermediate increase with haloperidol and a large increase with RIS (David et al., 2000). Fraguas et al. also

Table 2
Differences in plasma prolactin levels among 5 second-generation antipsychotics.

		Olanzapine	Risperidone	Aripiprazole	Quetiapine	Perospirone	P value
Dose	mg/day	19.6 ± 9.3	4.6 ± 2.5	20.1 ± 8.4	557.6 ± 171.4	29.2 ± 15.6	
CP equivalence[a]	mg/day	783.3 ± 371.5	451.4 ± 250.1	501.5 ± 209.8	844.8 ± 259.8	365.4 ± 194.8	P<0.001
Age[a]	Years	35.5 ± 11.2	33.1 ± 12.9	33.7 ± 11.7	34.9 ± 10.7	36.4 ± 13.7	n.s.
Sex[b]	Male/female	39/33	38/32	27/40	12/21	17/9	n.s.
Body mass index[a]	kg/m2	22.6 ± 3.6	22.9 ± 5.9	21.5 ± 4.4	22.0 ± 3.3	20.7 ± 2.9	n.s.
Plasma prolactin level[c]	ng/ml						
All		32.7 (5.1–173.5)	63.3 (0.6–500.5)	3.5 (0.3–22.5)	16.3 (0.3–89.4)	6.6 (1.1–44.3)	P<0.001
Male		25.8 (5.1–64.1)	33.5 (0.6–186.7)	0.9 (0.3–9.9)	10.6 (0.3–42.3)	7.8 (1.1–44.3)	P<0.001
Female		65.9 (6.8–173.5)	89.4 (32.8–500.5)	7.8 (0.5–22.5)	19.3 (4.6–89.4)	5.3 (3.3–33.1)	P<0.001

Abbreviations: CP = chlorpromazine.
[a] Treatment groups were compared with a one-way analysis of variance, and values are expressed as mean ± SD.
[b] Chi-square test was used to compare.
[c] Treatment groups were compared with Kruskal–Wallis test, and values are expressed as median and (range).