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Prolactin and macroprolactin levels in psychiatric patients receiving atypical antipsychotics: A preliminary study

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ABSTRACT

The aims of this study were to clarify whether atypical antipsychotics can elevate serum levels of both macroprolactin and prolactin, and whether the macroprolactin levels differ according to the type of atypical antipsychotic being taken. In total, 245 subjects were enrolled consecutively in 6 hospitals. Serum prolactin and macroprolactin levels were measured at a single time point during maintenance antipsychotic monotherapy. The mean total serum prolactin levels including macroprolactin were 11.91, 20.73, 16.41, 50.83, 12.84, and 59.1 ng/mL for patients taking aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, and risperidone, respectively, while those for macroprolactin were 1.71, 3.86, 3.73, 7.28, 2.77, and 8.0 ng/mL. The total prolactin and macroprolactin levels were significantly higher among those taking paliperidone and risperidone than among those taking any of the other antipsychotics ($p < 0.01$). Moreover, there was a strong positive correlation between serum levels of prolactin and macroprolactin. Sexual dysfunction was reported in 35.5% (87/245) of the total subjects. However, the total prolactin level did not differ significantly between subjects with and without sexual dysfunction except gynecomastia. These findings suggest that treatment with risperidone and paliperidone can induce hyperprolactinemia and macroprolactinemia in psychiatric patients.

1. Introduction

Atypical antipsychotics are better tolerated by patients than typical antipsychotics, regarding extrapyramidal symptoms. However, some atypical antipsychotics (e.g., risperidone, paliperidone, and amisulpride) cause hyperprolactinemia, which like typical antipsychotics can cause certain adverse effects (Aboraya et al., 2004; Brunelleschi et al., 2003; Lee et al., 2012; Skopek and Manoj, 2010; Voicu et al., 2013). The adverse effects of antipsychotic-induced hyperprolactinemia include galactorrhea, gynecomastia, menstrual irregularities, sexual dysfunction, and osteoporosis (De Hert et al., 2014; Peveler et al., 2008). Especially, antipsychotic-induced sexual dysfunction is very negatively affects the quality of life and self-esteem (Baggaley, 2008). Some studies found that higher prolactin levels are positively correlated with a higher risk of sexual dysfunction. However, most studies failed to demonstrate an association between hyperprolactinemia and sexual dysfunction (De Hert et al., 2014). Especially, the report of the high prevalence of asymptomatic hyperprolactinemia led investigators to question this association (Johnsen et al., 2008).

Some investigators now suggest that screening of macroprolactinemia is important for the differential diagnosis of hyperprolactinemia to avoid unnecessary examinations and treatments (Fahie-Wilson and Smith, 2013). Some studies reported that macroprolactin essentially comprises a complex of prolactin with immunoglobulin G, and especially antiprolactin autoantibodies (Shimatsu and Hattori, 2012). However, the origin of macroprolactin remains unclear. Some studies examining a large number of patients revealed no specific association between macroprolactin and autoimmune disorders (Blanco-Favela et al., 2001; Ram et al., 2004). Thus, it is likely that autoimmune mechanisms

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may be directed mainly toward prolactin molecule in macroprolactinemia (Shimatsu and Hattori, 2012). Macroprolactinemia does not seem to induce hyperprolactinemia-related adverse effects due to the low bioactivity of macroprolactin (Leslie et al., 2001). Thus, when the etiology of hyperprolactinemia is a high serum macroprolactin concentration, additional evaluation and treatment for hyperprolactinemia is futile. In addition, it is possible that asymptomatic hyperprolactinemia is associated with macroprolactinemia. Thus, it was hypothesized that hyperprolactinemic patients without sexual dysfunction have high level of macroprolactin.

However, no studies have accurately measured the levels of macroprolactin in patients receiving antipsychotics, although some studies have used the polyethylene glycol (PEG) precipitation method to identify the existence of macroprolactin (Johnsen et al., 2008; Tschoner et al., 2009). The aims of the present study were thus to determine whether atypical antipsychotics can elevate serum levels of both macroprolactin and prolactin, whether there is any relationship between macroprolactin, prolactin, and sexual dysfunction and whether serum macroprolactin levels differ according the sort atypical antipsychotic being taken. To the best of our knowledge, this is the first preliminary study to measure and compare serum macroprolactin levels using an ELISA method in patients with psychosis who are medicated with various atypical antipsychotics.

2. Methods

2.1. Participants

In total, 245 subjects who met the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition for schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD) with psychotic features, brief psychotic disorder, and psychotic disorder, not otherwise specified (NOS) were enrolled consecutively in 6 hospitals. This cross-sectional study was conducted between 2011 and 2013. The patients were divided into 6 groups according to the antipsychotic agent that they had been already taking before the participation of this study: aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, or risperidone. In addition, all subjects had been taking the same dosage of an atypical antipsychotic for at least 2 weeks during maintenance antipsychotic monotherapy when they participated in this study. Subjects with comedications that could affect prolactin levels, except anticonvulsants, benzodiazepine, and antidepressants, were excluded from the study. Written informed consent to participate was obtained from all patients before beginning the investigation, and the applied protocol was approved by the institutional review board of each hospital.

2.2. Assessments

Serum prolactin and macroprolactin levels (hereafter referred to as prolactin and macroprolactin levels) were measured at a single time point (i.e., in a cross-sectional design) at the six participating hospitals. A blood sample was taken in the morning and then centrifuged to separate the serum. All blood samples at each hospital were moved to and analyzed in a single laboratory in order to avoid the potential variations between measurement equipment between the different hospital laboratories. In addition, information on prolactin-associated symptoms were recorded, such as the presence of galactorrhea, menstrual irregularity, amenorrhea, gynecomastia, diminished sexual desire, erectile dysfunction, and orgasmic dysfunction.

2.3. Measurements of prolactin and macroprolactin

The microtiter plate provided in the macroprolactin kit (Human Macroprolactin ELISA Kit, MyBioSource, USA) had been precoated with an antibody specific to macroprolactin. Serum samples were added to the appropriate microtiter plate wells with a horseradish-peroxidase-conjugated antibody and then incubated. Substrate solutions were then added to each well. The enzyme–substrate reaction was terminated by the addition of a sulfuric acid solution, and the resulting color change was measured spectrophotometrically at a wavelength of 448–452 nm (SpectraMax 190, Molecular Devices, China). The concentration of macroprolactin in the samples was determined by comparing the optical density of the samples to the standard curve. The concentration of prolactin was measured using an automated chemiluminescence assay (Siemens, USA). The normal range for the prolactin level in the laboratory is 2.1–17.7 ng/mL for men, 2.8–29.2 ng/mL for nonpregnant premenopausal women, and 1.8–20.3 ng/mL for postmenopausal women.

The term “total prolactin” is used henceforth to refer to prolactin plus macroprolactin, and “free prolactin” is used to refer to total prolactin minus macroprolactin. In addition, macroprolactinemia was defined as a macroprolactin/total prolactin ratio of $\geq 30\%$. Furthermore, excess prolactin levels were divided into mild (≤ 50 ng/mL), moderate (51–75 ng/mL), severe (76–100 ng/mL), and extreme (> 100 ng/mL) (Serri et al., 2003).

2.4. Statistical analysis

The demographic and clinical variables, prolactin/macroprolactin levels, and frequencies of variables were analyzed using Student's *t* test (or Mann-Whitney test), ANOVA (or Kruskal Wallis test), the chi-square test, and Pearson's correlation. ANOVA and the post-hoc test were used to compare the prolactin and macroprolactin levels among the various atypical antipsychotic patient groups, and the chi-square test was used to determine whether the difference among groups was significant with respect to the frequency. A general linear model was also used while controlling for covariates. Correlation analysis using Pearson's correlation was carried out to establish definitively whether there was any significant correlation between macroprolactin and prolactin levels. All tests were two tailed, and group differences were considered to be significant when $p < 0.05$. Except where stated otherwise, the data are presented as mean $\pm$ SD values. All statistical analyses were carried out using the SAS 9.3 software package and SALT 2.5.

3. Results

In total, 245 subjects with schizophrenia, schizoaffective disorder, bipolar disorder, MDD with psychotic features, brief psychotic disorder, and psychotic disorder, not otherwise specified (NOS) were enrolled (Table 1). Of the 245 subjects, 121 were men. In the total sample of 245 patients, the mean total prolactin levels were 28.1. The prevalence of patients with hyperprolactinemia was 38.4% (94/245), while that of patients with macroprolactinemia was 20.8% (51/245). The range of macroprolactin levels was 0.5–14.2 ng/mL. Among those with hyperprolactinemia, the mean total prolactin was 59.1, while those for patients with normal prolactin levels was 8.9. Prolactin and macroprolactin levels were significantly higher in the females (34.28 ± 45.20 ng/mL; 5.00 ± 4.04 ng/mL) than in the males (21.85 ± 27.31 ng/mL; 3.99 ± 2.86 ng/mL) ($p = 0.01$; $p = 0.025$).

The mean total prolactin levels in the aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, and risperidone groups were 11.91, 20.73, 16.41, 50.83, 12.84, and 59.1 ng/mL, respectively

Table 1
Distribution of diagnosis according to the sort of atypical antipsychotics.

Antipsychotics		Aripiprazole (n=39)		Blonaserin (n=39)		Olanzapine (n=42)		Paliperidone (n=35)		Quetiapine (n=46)		Risperidone (n=43)	
Variables		N	%	N	%	N	%	N	%	N	%	N	%
Diagnosis	SPR	21	54	31	78	32	76	27	77	7	15	31	72
	BD	11	28	5	13	8	19	2	6	26	57	7	16
	PD	6	15	2	5	2	5	0	0	12	26	1	2
	SAD	1	3	0	0	0	0	6	17	1	2	2	5
	BPD	0	0	0	0	0	0	0	0	0	0	1	2
	PDN	0	0	2	5	0	0	0	0	0	0	1	2

Abbreviations: N; number, SPR; Schizophrenia, BD; Bipolar disorder, PD; psychotic depression, SAD; schizoaffective disorder, BPD; brief psychotic disorder, PDN; psychotic disorder NOS.

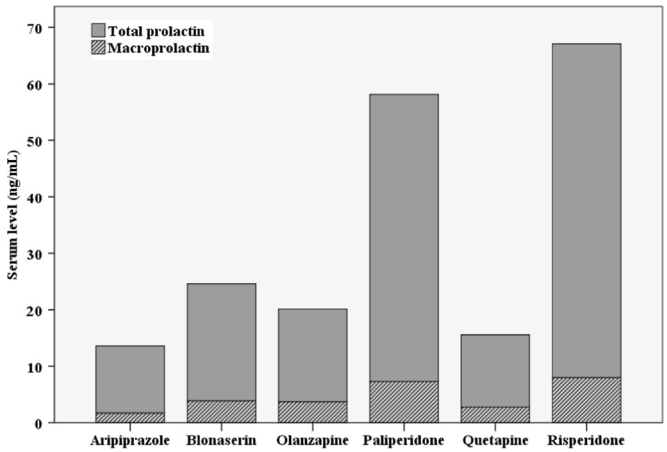

Fig. 1. The mean prolactin and macroprolactin levels in the aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, and risperidone groups differed significantly from one another ($p < 0.01$).

(Fig. 1; Table 2). These values were significantly different among six groups ($p < 0.01$) and this was maintained after controlling for age, treatment duration, and diagnosis ($p > 0.05$). On the contrary, these values were not significantly different after controlling sex ($p < 0.01$). The frequencies of patients with hyperprolactinemia were 10, 38, 29, 63, 15, and 79% in the aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, and risperidone groups, respectively. The mean macroprolactin level in the aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, and risperidone groups differed significantly from one another at 1.71, 3.86, 3.73, 7.28, 2.77, and 8.0 ng/mL, respectively (Fig. 1; Table 2). These values were also significantly different among six groups ($p < 0.01$) post-hoc analysis revealed that each risperidone group and paliperidone group had significantly higher levels of prolactin ($p < 0.01$) and macroprolactin ($p < 0.01$) than all of the other groups (Tukey post-hoc analysis). Moreover, there was a strong positive correlation between total prolactin and macroprolactin levels ($r = 0.76$, $p < 0.01$; Fig. 2).

The overall incidence of asymptomatic hyperprolactinemia was 31.9% (30/94). In addition, the number of patients with one or more prolactin-associated symptoms (amenorrhea, oligomenorrhea, menorrhagia, irregular menstruation, mastalgia, gynecomastia, decreased sexual drive, impotence, and organsmic dysfunction) was 87/245 (35.5%). The prolactin level did not differ significantly between those without and with (≥ 1) prolactin-associated symptoms (28.82 ± 38.92 vs 26.89 ± 36.12 ng/mL, $p = 0.704$). Three of the male patients reported gynecomastia, and all three of them had hyperprolactinemia (total prolactin, 92.02 ± 92.12 ng/mL; macroprolactin, 6.68 ± 3.71 ng/mL) and had taken either paliperidone or risperidone. Male sexual dysfunction was reported in 32.2% (39/121) of the male patients. The total prolactin level did not differ significantly between male subjects with and without sexual dysfunction (24.67 ± 37.92 vs 20.50 ± 20.61 ng/mL, $p = 0.423$). Among the female patients, 30 (24.2%) reported adverse effects with abnormal menstruation, such as amenorrhea and irregular menstrual cycles. Twenty patients with abnormal menstruation had a total prolactin level within the normal range, and the rest had increased total prolactin levels. The total prolactin level did not differ significantly between subjects with and without abnormal menstruation (29.44 ± 30.21 vs 35.82 ± 49.07 ng/mL, $p = 0.503$). Sexual dysfunction was reported in 38.7% (48/124) of the female patients. The total prolactin level did not differ significantly between female subjects with and without sexual dysfunction (28.70 ± 34.90 vs 37.80 ± 50.55 ng/mL, $p = 0.277$).

Excess total prolactin levels were divided into mild (≤ 50 ng/mL), moderate (51–75 ng/mL), severe (76–100 ng/mL), and extreme (> 100 ng/mL) (Table 3). However, measurement of free prolactin only, and not total prolactin, altered the severity of prolactin excess (Table 3).

4. Discussion

In the present study, the incidence of antipsychotic-induced hyperprolactinemia was 38.4% among those treated with atypical antipsychotic agents. In particular, the frequency of hyperprolactinemia was 63% in the paliperidone group and 79% in the risperidone group. In addition, the risperidone group and paliperidone group had significantly higher levels of prolactin and macroprolactin than all of the other groups. Intriguingly, the finding of a strong positive correlation between prolactin and macroprolactin levels suggests that the elevation in macroprolactin is due to the elevation in prolactin level. Sexual dysfunction was reported in 35.5% (87/245) of the total subjects.

While macroprolactin levels were measured in this study, the PEG precipitation method applied in previous studies was not utilized (Johnsen et al., 2008; Tschoner et al., 2009). The PEG precipitation method does not provide an accurate measure macroprolactin levels, but rather identifies only the existence of macroprolactin in the serum. The method used in the present study, which involves an antibody specific to macroprolactin, provides an accurate and direct measurement of macroprolactin in serum. However, it was found that both the prolactin and macroprolactin levels of patients with asymptomatic hyperprolactinemia did not differ from those of patients with symptomatic hyperprolactinemia. The range of macroprolactin values was 0.5–14.2 ng/mL, and the mean macroprolactin level was 4.5 ng/mL. Thus, contrary to the study hypothesis, macroprolactin did not influence prolactin-associated symptoms. However, a particularly interesting finding was that measurement of free prolactin only, and not total prolactin, altered the severity of prolactin excess. For

Table 2
Comparison among groups receiving each atypical antipsychotic.

Antipsychotics	Aripiprazole (n=39)		Blonaserin (n=39)		Olanzapine (n=42)		Paliperidone (n=35)		Quetiapine (n=46)		Risperidone (n=43)		*F*	*df*	ANOVA
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			*P*-value
Age (years)	34.59	11.47	37.88	13.14	46.19	15.21	40.97	14.66	46.78	15.42	42.53	10.74	5.03	5	<0.01
Height (cm)	163.92	7.56	166.12	5.47	165.07	9.57	165.86	9.2	164.51	8.94	163.66	8.05	0.58	5	0.72
Weight (kg)	65.77	10.66	66.78	9.94	69.09	9.67	71.11	15.3	66.67	17.12	70.18	13.83	1.05	5	0.39
BMI (kg/m^2)	24.48	3.45	24.19	3.36	25.36	2.94	25.73	4.34	24.46	5.02	26.11	4.34	1.56	5	0.17
Age of onset (years)	27.55	10.87	26.95	8.43	33.02	14.74	29.85	13.96	37.89	15.03	28.86	11.14	4.53	5	<0.01
Duration of illness (years)	7.24	5.39	11.13	8.67	13.61	10.01	11.27	6.61	8.39	8.21	14.58	9.57	4.83	5	<0.01
Total Tx duration (month)	43.44	65.15	67.97	66.68	88.31	80.56	69.8	65.23	68.83	71.97	110.29	94.45	2.95	5	<0.05
Current tx duration (month)	6.92	10.93	3.43	3.6	16.82	21.94	10.35	11.13	8.64	13.94	14.2	18.06	4.53	5	<0.01
Dosage (mg)	15.21	9.62	12.7	6.27	13.69	6.68	7.03	3.63	361.96	308.7	4.52	3.45	NA	NA	NA
CPZ equivalent (mg)	202.51	127.82	213.35	103.66	289.29	162.13	234.29	121.13	292.5	247.16	291.28	287.59	1.99	5	0.081
Prolactin (mg/dl)	11.91	21.58	20.73	16.9	16.41	14.44	50.83	57.64	12.84	15.79	59.1	48.9	88.86	5	<0.01*
Macroprolactin (mg/dl)	1.71	1.48	3.86	2.54	3.73	2.3	7.28	3.35	2.77	2.17	8	3.88	101.1	5	<0.01*
Free prolactin (mg/dl)	10.21	21.27	16.87	15.13	12.68	12.43	43.77	55.63	10.07	14.06	51.1	45.6	82.68	5	<0.01*
Comedication	(N)	(%)	(N)	(%)	(N)	(%)	(N)	(%)	(N)	(%)	(N)	(%)	NA	NA	NA
Mood stabilizer	14	35.9	16	41	13	31	14	40	23	50	18	41.9			
Antidepressant	13	33.3	12	30.8	9	21.4	14	40	27	58.7	7	16.3			
Benzodiazepine	10	25.6	24	61.5	15	35.7	12	34.3	23	50	25	58.1			
No comedication	14	35.9	8	20.5	14	33.3	7	20	2	4.3	9	20.9			

Abbreviation: NA, nonavailable; Tx, treatment.

* Kruskal Wallis test.

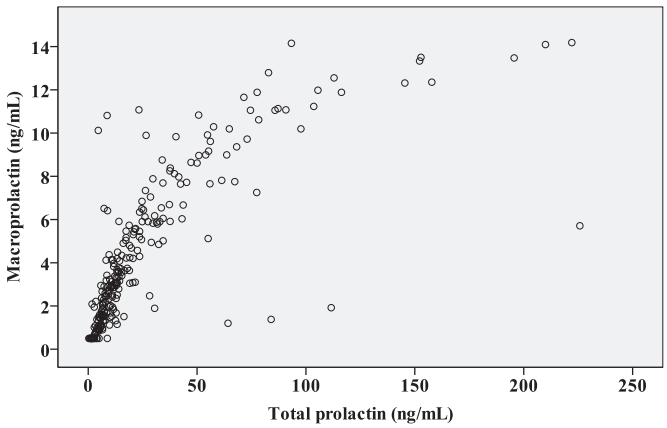

Fig. 2. Positive correlation between total prolactin and macroprolactin.

Table 3
Distribution in severity of hyperprolatinemia based on total prolactin or free prolactin level difference in distribution of total prolactin or free prolactin level.

Variables		Total prolactin levels (ng/mL)				
Prolactin range		Normal range	≤50	51–75	76–100	>100
Free prolactin levels (ng/mL)	Normal range	151	21	0	0	
	≤50		32	9	0	
	51–75			9	5	
	76–100				5	2
	>100					11

example, the original number of patients with total prolactin levels of 51–75 ng/mL was 18, but after removing macroprolactin level from total prolactin, only 9 patients had free prolactin levels of 51–75 ng/mL; the free prolactin of the other nine patients decreased to ≤50 ng/mL (Table 3). This represents a clinically very important finding because the treatment strategy differs according to a prolactin cutoff value of 50 ng/mL. Active correction of hyperprolactinemia, such as medication change, dosage reduction, and application of a dopamine agonist, is not considered for a prolactin level of ≤50 ng/mL unless persisting adverse effects including sexual dysfunction and decreased bone mineral density persist. Conversely, active correction is absolutely required for prolactin values of >50 ng/mL (Peveler et al., 2008). When this treatment strategy is applied for our data, among patients with total prolactin levels of 51–75 ng/mL, according to the total prolactin levels, 18 patients need to be treated, but using the free prolactin levels, only 9 patients need to be treated. Thus, free prolactin and macroprolactin levels seem to be clinically very important.

As reported elsewhere (Inder and Castle, 2011), atypical antipsychotic-induced hyperprolactinemia is a common adverse effect. Moreover, it has been demonstrated that long-term hyperprolactinemia induces loss of bone density and can be associated with pituitary tumors, breast cancer, and prostate cancer (Peveler et al., 2008). Nevertheless, hyperprolactinemia and the associated clinical symptoms have been neglected in clinical practice compared with antipsychotic-induced extrapyramidal symptoms (Kohen and Wildgust, 2008). Moreover, some practice guidelines recommend the prolactin level to be measured only in the presence of hyperprolactinemia-associated symptoms (Johnsen et al., 2008). However, it has been reported that the incidence of asymptomatic hyperprolactinemia is high (49%) (Johnsen et al., 2008). Consistent with that finding, the incidence of asymptomatic hyperprolactinemia in the present study was 31.9%. Thus, monitoring of prolactin only when there are prolactin-associated symptoms may lead to missing patients with asymptomatic hyperprolactinemia. Regular monitoring of prolactin is also considered essential for patients receiving antipsychotics with prolactin-increasing potential, such as risperidone, paliperidone, and amisulpride (Haddad and Wieck, 2004); however, current study revealed even aripiprazole induced high prolactin levels (111.6 ng/mL) in one patient like previous report (Saraf et al., 2014), although the mean total prolactin level was very low in their sample. In addition, Since there are a relatively high number of patients with spontaneous hyperprolactinaemia, as demonstrated in unmedicated patients (Albayrak et al., 2014), and the current study is cross-sectional, a direct relation between a prolactin level of 111.6 and aripiprazole treatment cannot be concluded.

In line with previous results (Johnsen et al., 2008; Kinon et al., 2003), prolactin levels were higher in the female patients than in the male patients in the present study ($p=0.01$). Macroprolactin levels were also significantly higher in the females than in the males ($p=0.025$). After controlling for sex, mean prolactin and macroprolactin levels were not significantly different among six groups. These means that female patients were more vulnerable to the antipsychotic-induced hyperprolactinemia than male patients.

The total prolactin level did not differ significantly between subjects with and without sexual dysfunction, a finding that is supported by most previous studies (De Hert et al., 2014). However, the total prolactin level did differ significantly between subjects with and without gynecomastia. Thus, gynecomastia appears to differ from other parameters of sexual dysfunction, which in addition to prolactin, is influenced by dopamine, acetylcholine, and the adrenaline system (Krause, 2012).

Antipsychotic-induced hyperprolactinemia is related to differential D2 receptor affinity, 5-hydroxytryptamine receptor affinity, and blood–brain disposition of antipsychotics (Fitzgerald and Dinan, 2008). In particular, Kapur and colleagues (Kapur et al., 2002) reported that the presence of different concentrations of antipsychotics in the pituitary gland and striatum lead to hyperprolactinemia. For example, risperidone has poor blood–brain penetration, and high concentrations of risperidone exist in the pituitary (Kapur et al., 2002). In line with that previous study, risperidone and paliperidone appeared to increase prolactin levels in this study much more than the other atypical antipsychotics, including aripiprazole, quetiapine, and olanzapine. In addition, prolactin levels were lower with blonanserin than with either risperidone or paliperidone, although the D2 affinity of blonanserin is very high (Tenjin et al., 2013).

This study has several limitations. The validation of this ELISA method has not been established yet. In addition, preantipsychotic baseline prolactin levels were not measured due to the cross-sectional study design, which makes it difficult to demonstrate causal relationships. The sample comprised heterogeneous patients with various diseases including schizophrenia, bipolar disorder, schizoaffective disorder, MDD with psychotic features, brief psychotic disorder, and psychotic disorder, NOS. However, since medical disorders or conditions and comedications known to affect prolactin were excluded, it was possible to evaluate antipsychotic-induced hyperprolactinemia. In addition, all of the subjects had taken the same dosage of atypical antipsychotics for at least 2 weeks during maintenance antipsychotic monotherapy at the time their blood was sampled. Furthermore, prolactin levels are known to be persistently elevated from 72 h after the initiation of treatment, decreasing rapidly to normal within 48–96 h after discontinuation of the antipsychotic drug (Meltzer and Fang, 1976). Thus, it is unlikely that previous antipsychotics had affected the prolactin levels in the population included in the present study. The use of comedication including mood stabilizer, antidepressant, and benzodiazepine is also limitation as it is unknown whether

that affects the level of macroprolactin. In addition, a validated rating scale was not used for information on hyperprolactinaemia-associated symptoms.

This is the first preliminary study to have examined the macroprolactin levels in patients with psychosis who received atypical antipsychotic therapy. The present findings suggest that atypical antipsychotic treatment such as risperidone and paliperidone can induce hyperprolactinemia and macroprolactinemia in patients with psychosis. Clinicians should measure and monitor serum prolactin levels in these patients; macroprolactin measurement also seems to be necessary in some patients with hyperprolactinemia.

Conflict of interest

All authors declare that there are no financial conflict of interest.

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