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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