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Add-on effects of a low-dose aripiprazole in resolving hyperprolactinemia induced by risperidone or paliperidone

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ABSTRACT

This study investigated the effects of a low-dose aripiprazole adjunctive treatment for risperidone- or paliperidone-induced hyperprolactinemia in Han Chinese women with schizophrenia. After 4 weeks of risperidone or paliperidone treatment, 60 out of 66 patients improved significantly and experienced hyperprolactinemia. They were randomly assigned to the treatment group (aripiprazole adjunctive treatment) ($n=30$) or control group (non-adjunctive treatment) ($n=30$). The dosage of risperidone and paliperidone were maintained; and aripiprazole was maintained at 5 mg/day during the 8-week study period. The prolactin levels at the end of the 8th week were significantly lower in the treatment group than in the control group. The estradiol level correlated negatively with serum prolactin level both in the treatment group and the control group at the end of the 8th week and the 4th week respectively. The Positive and Negative Syndrome Scale score improved significantly during the 8-week study period in both groups. The incidence of treatment-emergent adverse event was similar in two groups. Low-dose aripiprazole adjunctive treatment is effective in relieving risperidone- and paliperidone-induced hyperprolactinemia in female schizophrenic patients without increasing adverse event.

1. Introduction

Antipsychotic-induced hyperprolactinemia is a well-recognized neuroendocrine response to antipsychotics, particularly in female patients (Seeman, 2004), with the prevalence rates varying from 42% to 89% across different study samples (Halbreich and Kahn, 2003; Johnsen et al., 2008; Melkersson, 2005; Wang et al., 2013). Hyperprolactinemia has short and long-term side effects including sexual dysfunction, menstrual irregularities, amenorrhea, galactorrhea, gynecomastia, infertility, osteoporosis, and breast cancer (Holt and Peveler, 2010). Unfortunately, despite the high prevalence (Kinon et al., 2003), antipsychotic-induced hyperprolactinemia is less successfully managed, leaving potential harmfulness to patients' life (Lu et al., 2008).

Among schizophrenic patients treated with second-generation antipsychotics, hyperprolactinemia are more likely to be associated with risperidone and paliperidone (Byerly et al., 2007; Haddad and Wieck, 2004; Holt and Peveler, 2010; Peuskens et al., 2014; Wang et al., 2013). This may probably be due to their high affinity for dopamine D2 receptor and their permeability through blood brain barrier (Madhusoodanan et al., 2010; Torre and Falorni, 2007). Aripiprazole is a potent partial agonist at the dopamine D2, which did not cause hyperprolactinemia and even reduces serum prolactin levels below placebo levels (Peuskens et al., 2014; Tadori et al., 2008). Switching from antipsychotics that increase prolactin levels to aripiprazole or decreasing the antipsychotics doses is effective in resolving antipsychotic-induced hyperprolactinemia, yet with the potential risk of worsening the psychotic symptoms in some schizophrenic patients (Glick et al., 2006; Lee et al., 2006; McCue et al., 2006; Rocha et al., 2010). Studies have shown that combined treatment with flexible dosage aripiprazole (5–15 mg/day) and risperidone (Chen et al., 2009) can decrease prolactin concentration without worsening the psychotic symptoms (Chen et al., 2009; Kane et al., 2009; Lee et al., 2006; Yasui-Furukori et al., 2010). Given the observation that the dosages of aripiprazole are independent of the reduction ration of plasma prolactin concentration (Yasui-Furukori et al., 2010), low dosage adjunctive aripiprazole treatment may be a preferable strategy to decrease hyperprolactinemia induced by antipsychotics

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(Centorrino et al., 2004; Fleischhacker and Uchida, 2012), however, this requires investigation.

Menstrual irregularities including amenorrhea and dysmenorrhea are common side effects of antipsychotics treatment among female patients with the prevalence of up to 45% (Goffin et al., 2002; Haddad and Wieck, 2004). Although hyperprolactinemia and hypoestrogenism are associated with the increased risk of menstrual irregularities in schizophrenic women (Clevenger et al., 2003; Holt and Peveler, 2010; Klibanski et al., 1980; Knegtering et al., 2003), the results remain elusive. Studies showed that among female schizophrenic patients treated with antipsychotics, menstrual irregularities and hyperprolactinemia may occur with (Kinon et al., 2003) or without low serum estradiol level (Konarzewska et al., 2009). On the other hand, hypoestrogenism in schizophrenia occurs in women with and without antipsychotic-induced hyperprolactinemia (Bergemann et al., 2005). The relationship between serum prolactin levels and serum estradiol level in female schizophrenic patients needs further investigation. Despite a previous case report (Rocha et al., 2010), studies on whether paliperidone-induced hyperprolactinemia could be reversed or attenuated by the addition of aripiprazole are not common. Furthermore, most of the previous studies were focused on the Western population, and we know little about the effect of adjunctive aripiprazole treatment on antipsychotic-induced hyperprolactinemia in Han Chinese schizophrenic patients.

This 8 weeks prospective open-label randomized controlled study evaluates the effectiveness of add-on effects of aripiprazole in reducing risperidone- and paliperidone-induced hyperprolactinemia in Han Chinese female schizophrenic patients. We also examined the association between hyperprolactinemia and serum estradiol level.

2. Methods

The study protocol was reviewed by the ethical committee of Shanghai Mental Health Center and was performed under the ethical principles laid down by Good Clinical Practice and the Declaration of Helsinki. All subjects and/or their authorized legal representatives were informed of the purpose of the study and written informed consent was obtained. Chinese Clinical Trial Register Identifier: ChiCTR-TRC-14004186.

2.1. Subjects

Nonpregnant, nonlactating female inpatients 18–45 years of age with a DSM-IV diagnosis of schizophrenia, were eligible for the study. Subjects were required to have a total Positive and Negative Syndrome Scale (PANSS) score between 60 and 120 (inclusive). Major exclusion criteria were: serum prolactin levels greater than 496 mUI/L; current DSM-IV axis I psychiatric diagnosis other than schizophrenia, any neurologic disorder, severe head trauma, or any unstable medical condition, and history of substance dependence.

2.2. Study design

The study was conducted in Shanghai Mental Health Center from July, 2012 to May, 2014. Sixty-six female patients were enrolled for 4-week risperidone or paliperidone antipsychotic mono-antipsychotic drug treatment. All patients were either medication naïve, or did not take antipsychotic medicine for at least 2 weeks before the enrollment. Study drugs were administered orally, once (QD, morning) for paliperidone or twice (BID, afternoon and evening meal) for risperidone daily, after noon and evening meal. Risperidone and paliperidone were started at 1 mg/day and 3 mg/day respectively. Dosage could be titrated to 6 mg/day and 12 mg/day during the first two weeks. The dosage was 3–6 mg/day for risperidone and 6–12 mg/day for paliperidone from the third week till the end of the study. Modified electroconvulsive therapy (MECT) was administered during the 4-week period if mono-antipsychotic drug treatment was not effective enough to relieve symptoms according to the patient's individual situation. The MECT was conducted 8 standard treatments using a brief pulse, constant current apparatus with the electrode placed as bi-frontotemporal location during the 4-week period. Anesthesia was induced with propofol (2 mg/kg) or etomidate (0.3 mg/kg).

All raters (2 psychiatrists and 2 residents) had read through the PANSS manual and used the videotaped instructional material made by Shanghai Mental Health Center. The study groups held 3 sessions and 3 patients were interviewed at 2-week interval. The intraclass correlation coefficient for the total PANSS score was 0.90.

Sixty female patients (90.9%) improved significantly (PANSS score decreasing $\geq 50\%$) and experienced hyperprolactinemia (PRL $\geq$ 496 mIU/L) after antipsychotic treatment with or without MECT at the end of the fourth week. The average age of patients was 33.3 (SD = 6.9) years. The average drug dosage was 5.2 mg/day (SD = 1.4) for risperidone and 9.4 mg/day (SD = 2.0) for paliperidone. The mean serum prolactin level was 2938.0 mIU/L (SD = 1241.1). The mean PANSS score was 64.2 (SD = 13.8). The patients were then randomly assigned to the treatment (5 mg/day aripiprazole adjunctive treatment) group or the control (non-adjunctive treatment) group for another 8 weeks. Antipsychotic drug dosage was maintained as before and remained unchanged for the 8-week study period. Aripiprazole dosage was fixed at 5 mg/day, and continued until the end of the study; it was administered orally, once daily (QD) after the evening meal. No other medications that could alter prolactin levels were permitted. Clonazepam, as needed for anxiety or insomnia, was permitted. Artane was prescribed for patients if necessary for the treatment of extra pyramidal syndrome (EPS). The flow diagram of study is shown in detail in Fig. 1.

2.3. Assessments

Severity of psychopathology was assessed with the PANSS Scale. The efficacy measurement was the change in PANSS total score from baseline to the end of 4th and 8th week after random assignment. Adverse events were monitored by Treatment Emergent Symptom Scale (TESS) from baseline to the endpoint. Fasting clinical laboratory testing (including hematology, serum chemistry, prolactin levels and urinalysis), body weight, vital sign, electrocardiograms, and physical examination were also assessed at baseline and end of the study.

2.4. Serum prolactin and estradiol level

Blood was drawn at baseline, 2nd, 4th, 6th and 8th week after random assignment. A single fasting morning blood sample was obtained between 6:00 A.M. and 6:30 A.M. from all patients. Whole blood was collected and centrifuged to separate serum. Serum was stored in plastic tubes at $-80\,^{\circ}C$ until assays were completed. Study enrollment and monthly blood sampling were independent of patients' each month's menstrual cycle. Serum prolactin was measured at baseline, 2nd, 4th, 6th and 8th week. Serum estradiol was measured at baseline, 4th, and 8th week of the study period. Serum prolactin and estradiol levels were measured with electrochemiluminescent immunoassays, using commercial kits for measuring prolactin with sensitivity (Abbott Laboratories, Chicago, IL, USA). The coefficients of variations were 3.6–4.3 for prolactin and 2.1–3.3 for estradiol respectively. Hyperprolactinemia was defined as a serum level of $\geq$ 496 mIU/L