

Hypoprolactinemia and Extrapyrimal Symptoms in Male Schizophrenia or Psychotic Affective Disorder Patients Treated with Aripiprazole

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ABSTRACT

To investigate the plasma levels of prolactin during treatment with aripiprazole and their relationship to extrapyramidal symptoms (EPS), the levels of prolactin were measured and episodes of EPS were reviewed in 129 inpatients treated with aripiprazole or olanzapine. The mean level of prolactin in the aripiprazole group was significantly lower than that in the olanzapine group (male: 2.5 vs. 23.5; female: 5.8 vs. 38.4 ng/mL, $p < 0.01$). In the male aripiprazole subjects, a significant negative correlation between prolactin levels and the dosage was found ($p < 0.01$) and, at some (but not all) dosages, extrapyramidal symptoms occurred in the subjects with the lowest prolactin levels. These results suggest that aripiprazole could act as a “net antagonist” in the nigrostriatal pathway, and that the development of EPS may be associated with lower prolactin levels in male subjects. Simultaneously, aripiprazole acts as a strong dose-dependent “net agonist” in the tuberoinfundibular pathway, and causes severe hypoprolactinemia that may be associated with adverse events in aripiprazole monotherapy.

Keywords: *Aripiprazole, agonist, antagonist, extrapyramidal symptoms, hypoprolactinemia*

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INTRODUCTION

All currently available antipsychotic agents, both conventional and atypical, with the exception of D2 partial agonists, antagonize dopamine D2 receptors. D2 receptor blockade in the mesolimbic pathway is thought to mediate antipsychotic efficacy, which is the ability to decrease positive symptoms [1], whereas D2 receptor blockade in the mesocortical, nigrostriatal, and tuberoinfundibular pathways is associated with a dysfunctional reward system and increased tendency to develop extrapyramidal symptoms (EPS) and hyperprolactinemia, which are unwanted adverse reactions to antipsychotic therapy.

Aripiprazole is a potent (high-affinity) partial D2 agonist that exerts intrinsic activity on D2 receptors [2]. A D2 partial agonist is a logical strategy for the

treatment of schizophrenia due to excessive dopamine activity in some regions of the brain and inadequate dopamine activity in other regions. A D2 partial agonist is expected to act as a functional antagonist in areas of high levels of dopamine such as the mesolimbic pathway, and as a functional agonist in areas of low levels of dopamine such as the mesocortical pathway, not in areas of normal dopamine levels such as the nigrostriatal and tuberoinfundibular pathways [3]. However, could a partial D2 agonist really act on multiple pathways to obtain optimal dopamine levels in every situation?

From the fact that a large number of D2 spare receptors exist, particularly in the anterior pituitary [4], and the fact that, in ex vivo experiments, aripiprazole inhibited spontaneous prolactin release from isolated anterior pituitary slices [5], it is believed that aripipra-

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zole monotherapy may reduce plasma prolactin levels. The aim of the present study is to investigate plasma prolactin levels during treatment with aripiprazole, and their relationship to the appearance of EPS.

SUBJECTS AND METHODS

All inpatients administered aripiprazole or olanzapine continuously for more than two weeks with a diagnosis of schizophrenia or psychotic affective disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Text Revision were enrolled consecutively and studied retrospectively from April to December 2011 at Kusatsu Hospital in Hiroshima, Japan. The exclusion criteria included concomitant use of antipsychotics, antidepressants or antiparkinson drugs, as well as some medical conditions, such as thyroid dysfunction, that are believed to directly or potentially affect the dopamine system and prolactin levels. A total of 129 subjects were finally selected and divided into the aripiprazole or olanzapine monotherapy group. The aripiprazole group consisted of 32 men and 36 women with a mean age of 51 years, while the olanzapine control group consisted of 30 men and 31 women with a mean age of 49 years.

Plasma sample collection of fasting blood was performed after each dosage sequence, and measurements were performed by enzyme immunoassay (IMX Prolactin Dinapack, Dinabot Ltd., Tokyo,

Japan). The prolactin references ranges were 3.57 to 12.78 ng/mL for men and 6.12 to 30.54 ng/mL for women. The detection limit was 0.06 ng/mL.

Differences in prolactin levels between the aripiprazole and olanzapine groups in each gender were evaluated using the unpaired Mann-Whitney U test, and considered statistically significant at $p < 0.05$. Within each treatment subgroup, the data were analyzed to see whether there was any significant correlation between prolactin levels and the dosage using the Spearman's correlation coefficients method and considered statistically significant at $p < 0.05$. Moreover, episodes of EPS were investigated in all subjects during the treatment period. To evaluate EPS, a second-generation rating scale for antipsychotic-induced extrapyramidal symptoms – DIEPSS – was used [6]. In this study, the “overall severity” scale was used to determine the “EPS” grades.

This study was approved by the ethics committee of Kusatsu Hospital, and informed consent was obtained from all participants.

RESULTS

In both males and females, the prolactin concentrations were significantly lower in the aripiprazole group than in the olanzapine group (males: 2.5 ± 0.3 vs. 23.5 ± 2.7 , $p < 0.01$; female: 5.8 ± 0.7 vs. 38.4 ± 5.1 , $p < 0.01$; mean \pm SE) (Figure 1).

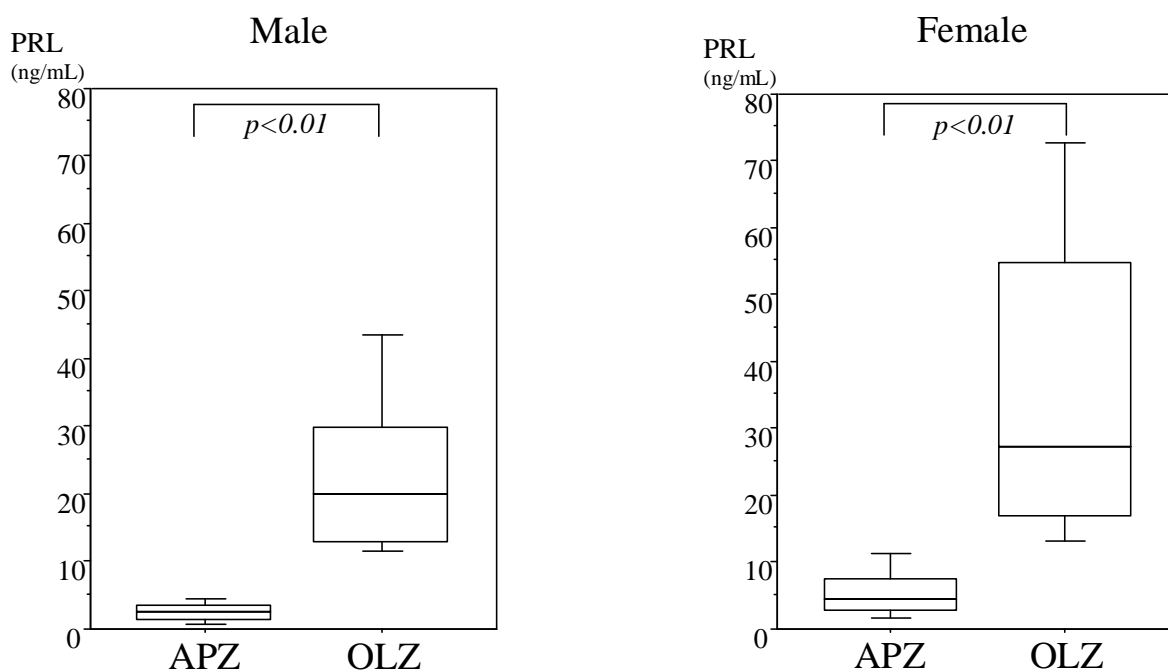


Fig. 1. Plasma levels of prolactin (PRL) in male and female subjects treated with aripiprazole (APZ) and olanzapine (OLZ)

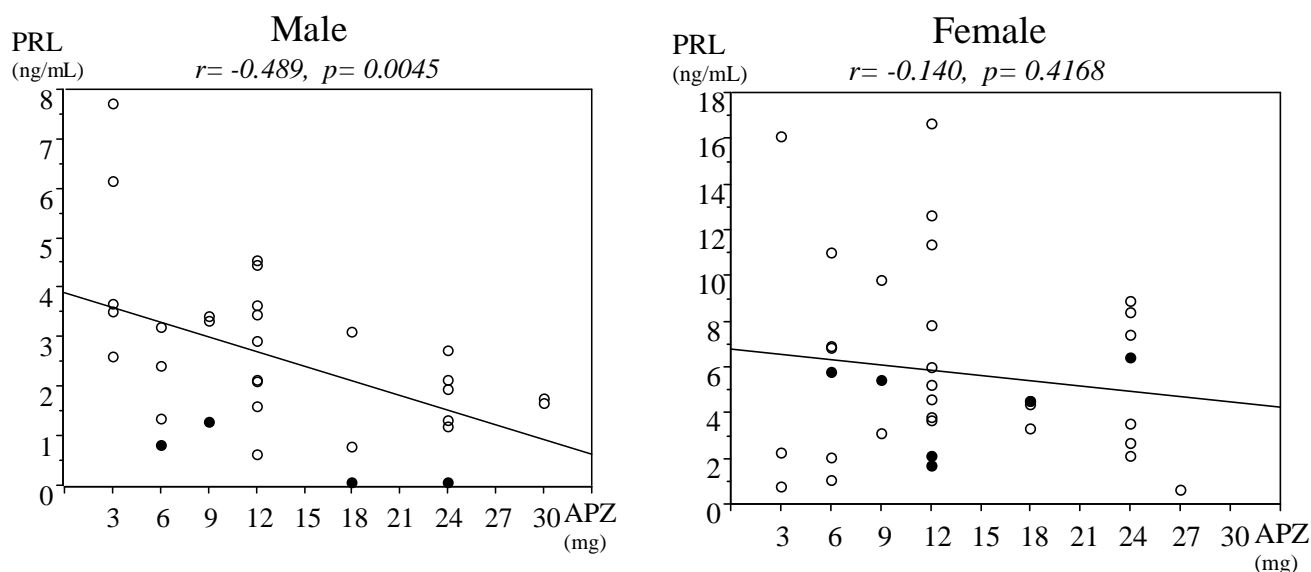


Fig. 2. Correlation between plasma levels of prolactin (PRL) and the aripiprazole (APZ) dosage in male and female subjects
White circles indicate subjects who did not experience extrapyramidal symptoms (EPS) and black circles indicate subjects who experienced EPS.

In the aripiprazole group, prolactin levels below the lower reference limit were found in 26 out of 32 males and 26 out of 36 females, whereas in the olanzapine group, all of the prolactin levels were above the lower reference limit.

There was a significant correlation between prolactin levels and the dosage only in the males in the aripiprazole group (Figure 2); in the females in the aripiprazole group, and in the olanzapine group overall, no such correlation was found.

Episodes of EPS occurred only in the aripiprazole group (in 4 out of 32 males and 6 out of 36 females). In the subjects with EPS, 8 subjects had EPS scores of 3 (moderate) and 2 subjects had EPS scores of 4 (severe). All of these subjects were switched to other antipsychotics. All of the subjects without EPS, however, had EPS scores of 0 (none). Akathisia occurred in one male and two females in the subjects with EPS. In the males in the aripiprazole group, at certain dosages, episodes of EPS were noted in the subjects with the lowest prolactin levels (0.83 ng/mL at 6 mg/day, 1.3 ng/mL at 9 mg/day, < 0.06 ng/mL at 18 mg/day, and < 0.06 ng/mL at 24 mg/day).

DISCUSSION

The results of this study suggested that monotherapy with aripiprazole significantly reduced prolactin plasma levels, although baseline levels were not

measured. Similar studies have been conducted before [7-10], but most involved adjunctive treatment with other antipsychotics or switching procedures, or were not conducted using strict exclusion criteria, or possibly without evaluating adherence. These studies may therefore not have proved any direct effect of prolactin levels much lower than the lower reference limit in treatment with aripiprazole.

The D2 receptor is a common target for antipsychotics, and the antipsychotic clinical doses correlate with their affinities for this receptor. Antipsychotics quickly enter the brain to occupy 60-80% of brain receptors in patients (the partial agonist aripiprazole occupies up to 90%), with most clinical improvement occurring within a few days [11]. Compared to olanzapine, which is relatively prolactin sparing, aripiprazole easily binds to D2 receptors and acts as an agonist in tuberoinfundibular pathways because of the large number of spare D2 receptors in the anterior pituitary [12]. The correlation between the plasma concentration of aripiprazole and the daily aripiprazole dose was demonstrated in the PET aripiprazole occupancy study, in which the D2 occupancy by aripiprazole correlated to the plasma concentration of aripiprazole [13]. This supports our results showing dosedependent prolactin levels in male subjects, who do not experience menstrual cycles or menopause. We could not observe this pattern in female subjects, perhaps because prolactin levels are periodically affected by

the levels of sex hormones (e.g., estrogen, progesterone).

It is interesting that EPS were observed at certain dosages in the male subjects with the lowest prolactin levels. Aripiprazole has a greater affinity for D2 receptors than intrinsic dopamine [14], and dissociates from them more slowly [15]. Moreover, aripiprazole has an intrinsic activity on dopamine D2 receptors [2]. Taken together, therefore, aripiprazole could act not as a “net agonist,” but a “net antagonist” in the nigrostriatal pathway, where the D2 receptor density is low, in cases of excessive D2 receptor occupancy. On the other hand, aripiprazole act as a strong agonist on D2 receptors and a “net agonist” in the tuberoinfundibular pathway, where the D2 receptor density is high, and induces severe hypoprolactinemia. To our knowledge, this is the first report suggesting that lower prolactin levels are related to the appearance of EPS in treatment with this partial dopamine agonist.

There are several limitations to this study. First, neither the duration of illness nor the previous antipsychotic medications were taken into account. Second, in a few of the subjects, the prolactin levels may not have been measured after a long enough treatment period, and the measured values were not adjusted for age or weight. Third, the definition of EPS in this study was limited to subjects who switched drugs according to a drug-induced extrapyramidal symptoms scale. Therefore, further study utilizing the long-term observation of individual subjects and evaluation of the before and after prolactin levels and EPS grades may be required to confirm our findings.

In conclusion, the results of our study suggest that aripiprazole causes dose-dependent hypoprolactinemia and that lower levels of prolactin are associated with the appearance of EPS in male subjects.

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