Relationship of Prolactin Concentrations to Steady-state Plasma Concentrations of Aripiprazole in Schizophrenia Patients

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Abstract

BACKGROUND: Aripiprazole is regarded as the first-line antipsychotic medication. Long-term aripiprazole therapy can cause hypoprolactinemia, which may result from its activity as a dopamine agonist. However, there is little information on hypoprolactinemia and steady-state aripiprazole concentrations.

METHODS: The subjects included 66 male and 177 female patients diagnosed with schizophrenia who were treated with aripiprazole. The plasma concentrations of aripiprazole and dehydroaripiprazole and the plasma concentration of prolactin were measured using high-performance liquid chromatography and enzyme immunoassay, respectively. A prolactin concentration of <5 ng/mL was defined as hypoprolactinemia.

RESULTS: Fifty-two of the 66 male patients (79%) and 58 of the 177 female patients (33%) had hypoprolactinemia. There were significant inverse correlations between plasma prolactin levels and plasma concentrations of aripiprazole ($r_s = -0.447$, $p < 0.001$) and the active moiety (aripiprazole plus dehydroaripiprazole) ($r_s = -0.429$, $p < 0.001$) in males. In females, significant inverse correlations were also found between plasma prolactin levels and plasma concentrations of aripiprazole ($r_s = -0.273$, $p < 0.01$) and the active moiety ($r_s = -0.275$, $p < 0.01$).

CONCLUSIONS: These findings suggest that lower prolactin levels are, to some extent,

associated with higher plasma drug concentrations in male and female patients with schizophrenia treated with aripiprazole.

Key Words

aripiprazole, dehydroaripiprazole, prolactin, schizophrenia

Background

Aripiprazole is a potent (high-affinity) partial dopamine D2 agonist, a serotonin 5-HT1A agonist, and a 5-HT2A antagonist. It acts as a functional antagonist at D2 receptors under hyperdopaminergic conditions but exhibits properties of functional agonists under hypodopaminergic conditions.[1] Because of this unique pharmacological profile, aripiprazole monotherapy has little effect on prolactin levels in patients with prior antipsychotic exposure and might actually lower the levels.[2,3] Several studies have suggested that patients treated with aripiprazole have relatively lower prolactin concentrations and that aripiprazole actually decreases prolactin levels.[4,5] In addition, plasma prolactin levels in the aripiprazole combination group were lower than those in the non-aripiprazole combination group, regardless of the antipsychotic monopharmacy or polypharmacy.[6]

Aripiprazole is metabolized by CYP2D6 and CYP3A4 to its pharmacologically active metabolite, dehydroaripiprazole, which is considered equipotent to the parent drug.[7] CYP2D6 genotypes influence the plasma concentrations of aripiprazole.[8,9,10] The consensus on the therapeutic range for aripiprazole, therefore, consists of the sum of the parent drug and the metabolite, which is the active moiety.[11] The plasma concentrations of dehydroaripiprazole are lower than those of aripiprazole after a single oral dose and at steady state.[12]

There have been few studies on the association between aripiprazole pharmacokinetics and reduced prolactin levels. In a previous study, no significant correlation between prolactin levels and the dose of aripiprazole was observed in 18 patients who received aripiprazole alone.[13] However, the sample size in that study was very small, which might have introduced a type II error. Therefore, we examined the effect of steady-state concentrations of aripiprazole on prolactin levels in Japanese patients with schizophrenia treated with aripiprazole monotherapy. In addition, we determined the effect of the sum of the parent drug and the metabolite on prolactin levels.

Materials and Methods

SUBJECTS

The subjects were 243 Japanese patients with schizophrenia (66 males and 177 females) who fulfilled the criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. The mean ± SD (range) body weight and duration of illness were 56.6 ± 11.6 (37–102) kg and 182 ± 138 (4–458) months, respectively. The mean ± SD ages were 37.3 ± 10.7 years for males and 39.9 ± 11.5 years for females. The study was approved by the Ethics Committee of Hirosaki University Hospital and Dokkyo Medical Hospital, and written informed consent to participate in this study was obtained from the patients.

PROTOCOL

The subjects received monotherapy with aripiprazole (Otsuka Pharma, Tokyo, Japan) 1–30 mg/day for 4–122 weeks. The mean ± SD aripiprazole doses were 11.9 ± 8.6 mg/day for males and 12.6 ± 8.4 mg/day for females. The elimination half-life of aripiprazole is approximately 75 and 94 h.[7] Steady-state serum levels are achieved within 14 days of dosing. Therefore, the plasma concentrations of aripiprazole had already reached a steady state in all the subjects before initiating the study. The mean ± SD daily dose for aripiprazole was 10.6 ± 7.7 mg for males and 12.4 ± 8.4 mg for females. The coadministered drugs were flunitrazepam 1–4 mg/day in 105 patients, diazepam 2–6

mg/day in 25 patients, lorazepam 1–3 mg/day in 12 patients, alprazolam 0.8–2.4 mg/day in 25 patients, biperiden 4–6 mg/day in 24 patients, and sennoside 12–48 mg/day in 56 patients.

ASSAYS

Plasma concentrations of aripiprazole and dehydroaripiprazole were measured using the high-performance liquid chromatography (HPLC) method developed in our laboratory.[14] The lowest limits of detection for aripiprazole and dehydroaripiprazole were 1.0 ng/mL. The intra - and inter-day relative SDs were less than 7.5% and 7.1% for aripiprazole and 9.2% and 4.5% for dehydroaripiprazole, respectively. Plasma prolactin concentration was determined using an electrochemiluminescence immunoassay (Elecsys Prolactin III, Roche Diagnostics, Tokyo, Japan). The lowest limit of detection was 0.4 ng/mL, and the interassay coefficients of variation (CVs) were 1.1%, 1.0%, and 1.3% at concentrations of 8.4, 24.9, and 56.4 ng/mL of prolactin, respectively. Pooled sera of 7 different low concentrations were prepared, and measurements were performed 10 times. A precision profile was prepared from the CV value of the measurement reproducibility, and a concentration within CV = 20% was set as the quantitation limit.

DATA ANALYSIS AND STATISTICS

Data are expressed as means ± SD. Comparisons of age, dose of aripiprazole, plasma concentrations of aripiprazole and dehydroaripiprazole, active moiety, and prolactin between males and females were performed using the Mann–Whitney *U* test and chi-squared test. Comparisons of the plasma concentrations of aripiprazole, active moiety, and prolactin level and the proportion of hypoprolactinemia were performed using ANOVA and the chi-squared test. Correlations between drug concentrations and prolactin concentrations were analyzed using the Spearman rank test because of the non-normal distribution of the concentrations of prolactin. A hyperbolic curve fitting analysis was also performed. All analyses were performed using the SPSS 25.0J software for Windows (SPSS Japan, Tokyo, Japan).

Results

The mean ± SD prolactin levels were significantly different ($p < 0.001$) between males (3.7 ± 3.2 ng/mL) and females (12.2 ± 14.9 ng/mL) (Table 1). Hyperprolactinemia was defined as a plasma prolactin concentration >20 ng/mL, and hypoprolactinemia was defined as a concentration <5 ng/mL.[15] Hypoprolactinemia occurred in 52 of 66 male patients (79%) and 58 of 177 female patients (33%). None of the male patients and 14 of

143 the 177 female patients (8%) had higher prolactin levels. The mean ± SD plasma
144 concentrations of aripiprazole, dehydroaripiprazole, and active moiety were 196 ± 170,
145 67.4 ± 51.2, and 263 ± 216 ng/mL in males and 160 ± 118 ng/mL, 60.1 ± 44.0, and 220 ±
146 116 ng/mL in females, respectively (Table 1).

147 We classified the patients into three groups: 1) plasma concentration of
148 aripiprazole <100 ng/mL, 2) plasma concentration of aripiprazole between 100 and 200
149 ng/mL, and 3) plasma concentration of aripiprazole >200 ng/mL. This classification was
150 based on Gruender et al.,[16] who demonstrated brain dopamine receptor saturation (90%
151 occupancy) at approximately 100 to 200 ng/mL of aripiprazole. There were significant
152 differences in prolactin concentrations and in the proportion of hypoprolactinemia among
153 the three groups in male and female patients (Table 2).

154 There were significant inverse correlations between plasma prolactin levels and
155 the concentrations of aripiprazole ($r_s = -0.447$, $p < 0.001$) or its active moiety (aripiprazole
156 plus dehydroaripiprazole) ($r_s = -0.429$, $p < 0.001$) in males (Fig. 1). In females, significant
157 inverse correlations were also found between plasma prolactin levels and the
158 concentrations of aripiprazole ($r_s = -0.273$, $p < 0.01$) and the active moiety ($r_s = -0.275$, p
159 < 0.01) (Fig. 1). A hyperbolic curve was found to significantly fit in males ($p < 0.001$),
160 but not in females ($p = 0.8$).

Discussion

The results of this study show, for the first time, an inverse association between prolactin and aripiprazole concentrations in men and women. However, the effect sizes in women were small. A high frequency of hypoprolactinemia was found in both men and women. The possibility that hypoprolactinemia merely represents therapeutic drug concentrations cannot be excluded. To confirm patient adherence, the measurement of prolactin concentration may alternatively be used. However, there is little information about the clinical relevance of hypoprolactinemia. In a study, it was shown that hypoprolactinemia is associated with metabolic syndrome and arteriogenic erectile dysfunction as well as with premature ejaculation and anxiety symptoms.[15] Several cases with insufficient milk production after aripiprazole treatment have been reported, which may be a problem for breastfeeding mothers.[17,18] Thus, it is possible that aripiprazole-induced hypoprolactinemia carries a potential health risk.

CYP2D6 and CYP3A4 metabolize aripiprazole,[7] and there are large interindividual variations in the activities of both these enzymes. Therefore, the steady-state plasma concentrations of aripiprazole and dehydroaripiprazole also have large interindividual variations.[12] Consequently, the plasma drug concentration might be a more suitable

179 variable to use than the drug dose when seeking to determine whether there is a correlation
180 with prolactin. The coadministration of a CYP3A4 inducer resulted in approximately 60%
181 lower mean C:D ratios of aripiprazole, dehydroaripiprazole, and the sum of aripiprazole
182 and dehydroaripiprazole. The combination with a CYP2D6 inhibitor resulted in a 45%
183 higher mean C:D ratio of aripiprazole ($p < 0.05$), with no effect on the C:D ratio of
184 dehydroaripiprazole.[19]

185 Gruender et al.[16] used PET to investigate the pharmacology of aripiprazole and
186 dopamine receptor occupancy and demonstrated brain dopamine receptor saturation (90%
187 occupancy) at approximately 100 to 200 ng/mL for aripiprazole. Our data support a
188 similar situation. Maximal effects were likely attained at approximately 200 ng/mL
189 aripiprazole in females and at approximately 100 ng/mL aripiprazole in males, which
190 suggests a sex difference in brain dopamine receptor saturation.

191 In a previous study, we showed that 59.3% of male and 49.1% of female patients with
192 schizophrenia experienced sexual dysfunction. High rates of low sexual interest (37.3%),
193 erectile dysfunction (37.3%), and problems related to ejaculation (35.6%) were observed
194 in males, and amenorrhea (38.7%) and low sexual interest (25.7%) were observed in
195 females.[20] A recent review suggested that 30%–82% of schizophrenic subjects aged 18–
196 70 years reported sexual dysfunction. Erectile dysfunction was the most common sexual

197 dysfunction in men with schizophrenia (31%–95% of male schizophrenic patients), and
198 31%–100% of women with schizophrenia reported a loss of libido.[21]

199 This study had several notable limitations. First, this study had a cross-sectional
200 design. We did not determine the degree of hypoprolactinemia because we had no baseline
201 prolactin data before the start of treatment with aripiprazole. The possibility that some
202 patients would have had hypoprolactinemia without treatment with antipsychotics,
203 including aripiprazole, cannot be excluded. In addition, we did not perform pituitary
204 function tests or brain imaging. Finally, we did not evaluate the symptoms of sexual
205 dysfunction. Therefore, we could not determine the aripiprazole treatment-induced effects
206 of hypoprolactinemia on sexual dysfunction. There are no data suggesting that long-term
207 exposure to aripiprazole-induced hypoprolactinemia results in adverse effects in patients
208 with schizophrenia. In addition, approximately 30%–40% of healthy subjects complain
209 of some sexual dysfunction.[20] Further studies are needed to overcome these limitations.

210

211 **Conclusion**

212 The present findings suggest that lower prolactin levels are partially associated
213 with higher plasma drug concentrations in male and female patients with schizophrenia
214 treated with aripiprazole. Further studies are needed to confirm these findings and their

clinical relevance.

References

1. Cada DJ, Levien T, Baker DE. Aripiprazole. *Hosp Pharm.* 2003;38:247-256.
2. Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology*. 2003;166:391-399.
3. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebocontrolled trials. *Schizophr Res*. 2003;61:123-136.
4. Yasui-Furukori N, Furukori H, Sugawara N, et al. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. *J Clin Psychopharmacol*. 2010;30:596-599.
5. Chen JX, Su YA, Bian QT, et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose-response study. *Psychoneuroendocrinology*. 2015;58:130-140.
6. Sugai T, Suzuki Y, Yamazaki M, et al. Lower prolactin levels in patients treated with aripiprazole regardless of antipsychotic monopharmacy or polypharmacy. *J Clin Psychopharmacol*. 2020;40:14-17.
7. Otsuka America Pharmaceutical, Inc. (2014) Abilify (aripiprazole) prescribing

information. Available at: http://www.abilify.com. Accessed Jul 08, 2014.

8. Tveito M, Molden E, Høiseth G, et al. Impact of age and CYP2D6 genetics on exposure of aripiprazole and dehydroaripiprazole in patients using long-acting injectable versus oral formulation: relevance of poor and intermediate metabolizer status. *Eur J Clin Pharmacol*. 2020;76:41-49.

9. Suzuki T, Mihara K, Nakamura A, et al. Effects of the CYP2D6*10 allele on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. *Ther Drug Monit*. 2011;33:21-24.

10. Belmonte C, Ochoa D, Román M, et al.. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. *Basic Clin Pharmacol Toxicol*. 2018;122:596-605.

11. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51:9-62.

12. Molden E, Lunde H, Lunder N, et al. Pharmacokinetic variability of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients. *Ther Drug Monit*. 2006;28:744-749.

13. Sogawa R, Shimomura Y, Minami C, et al. Aripiprazole-associated hypoprolactinemia in the clinical setting. *J Clin Psychopharmacol*. 2016;36:385-387.
14. Akamine Y, Yasui-Furukori N, Kojima M, et al. A sensitive column-switching HPLC method for aripiprazole and dehydroaripiprazole and its application to human pharmacokinetic studies. *J Sep Sci*. 2010;33:3292-3298.
15. Corona G, Mannucci E, Jannini EA, et al. Hypoprolactinemia: a new clinical syndrome in patients with sexual dysfunction. *J Sex Med*. 2009;6:1457-1466.
16. Gründer G, Fellows C, Janouschek H, et al. Brain and plasma pharmacokinetics of aripiprazole in patients with schizophrenia: an [18F]fallypride PET study. *Am J Psychiatry*. 2008;165:988-995.
17. Yskes R, Thomas R, Nagalla ML. A case of decreased milk production associated with aripiprazole. *Prim Care Companion CNS Disord*. 2018;20:18l02303.
18. Cuomo A, Goracci A, Fagiolini A. Aripiprazole use during pregnancy, peripartum and lactation. A systematic literature search and review to inform clinical practice. *J Affect Disord*. 2018;228:229-237.
19. Waade RB, Christensen H, Rudberg I, et al. Influence of comedication on serum concentrations of aripiprazole and dehydroaripiprazole. *Ther Drug Monit*. 2009;31:233-238.

20. Fujii A, Yasui-Furukori N, Sugawara N, et al. Sexual dysfunction in Japanese patients with schizophrenia treated with antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:288-293.

21. Dumontaud M, Korchia T, Khouani J, et al. Sexual dysfunctions in schizophrenia: Beyond antipsychotics. A systematic review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;98:109804.

Legend to the figure

FIGURE 1. Correlations between prolactin levels and plasma drug concentrations. Solid circles indicate data for males, and open circles indicate data for females. The active moiety is represented by the sum of the plasma concentrations of aripiprazole and dehydroaripiprazole. Because of the non-normal distribution of prolactin levels, Spearman rank tests (r_s) were used to determine the correlations.