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Improvement in antipsychotic-induced hyperprolactinemia with the addition of aripiprazole in schizophrenic patients

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ABSTRACT

Purpose: Hyperprolactinemia, a common adverse effect of antipsychotics, frequently impacts patients' quality of life. Aripiprazole is a potent dopamine D2 receptor partial agonist and rarely increases the serum prolactin concentration. The authors investigated the effect of aripiprazole coadministration on antipsychotic-induced hyperprolactinemia and associated symptoms in patients with schizophrenia.
Method: The subjects were 9 patients (8 females, 1 male) with hyperprolactinemia induced by risperidone, olanzapine, haloperidol, zotepine, bromperidol, levomepromazine, and quetiapine; 6 of the females had oligomenorrhea and 2 amenorrhea, and the male had erectile dysfunction. All of the patients received concomitant aripiprazole for more than 8 weeks at a mean dose (range) of 7.7 (3-18) mg/day. The doses of all other medications, including the hyperprolactinemia-inducing antipsychotics, remained fixed throughout the study period.
Results: The mean serum concentration (range) of prolactin during aripiprazole coadministration (29.9 (9.8-53) ng/ml) was significantly ($p=0.008$) lower than that before aripiprazole coadministration (81.1 (27-153) ng/ml). The associated symptoms were improved in 4 females (regularized or regained menstruation) and the male (normalized erectile function), while no changes were observed in the other clinical symptoms of schizophrenia.
Discussion: The results of the present study suggest that even small doses of coadministered aripiprazole effectively limit excessive prolactin response to antipsychotics without interfering with the benefits of existing prescriptions.

Keywords: hyperprolactinemia, aripiprazole, antipsychotics, schizophrenia

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INTRODUCTION

The dopamine D2 receptor in the anterior pituitary gland plays an inhibitory role in the regulation of prolactin secretion [1]. Antipsychotic drugs increase prolactin concentrations through the blockade of dopamine D2 receptors [1-3]. Hyperprolactinemia is a common but occasionally serious adverse effect of antipsychotic medication [1]. In the short-term, it can cause menstrual disturbances and/or galactorrhea in females and erectile dysfunction and/or loss of libido in males [1]. It has been shown that chronic hyperprolactinemia during long-term antipsychotic drug treatment is associated with an increase in

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breast cancer risk [4]. In addition, the risks of osteoporosis and hypogonadism have been highlighted due to long-term secondary estrogen deficiency caused by chronic hyperprolactinemia [5]. These adverse effects adversely impact patients' quality of life, leading to non-compliance with antipsychotic medication regimens.

Aripiprazole is a novel second-generation antipsychotic drug with a unique pharmacological profile of partial dopamine D2 agonism, partial 5-HT1A agonism, and 5-HT2A antagonism [6]. The efficacy and safety of aripiprazole have been established for the treatment of schizophrenia [7]. It has been shown that aripiprazole treatment rarely increases serum prolactin concentrations [8]. Interestingly, Shim et al. have reported that adjunctive aripiprazole treatment reversed hyperprolactinemia induced by haloperidol, and was beneficial for the treatment of menstrual disturbances induced by haloperidol [9].

Therefore, the authors investigated the effect of aripiprazole coadministration on hyperprolactinemia induced by various antipsychotics, and associated symptoms, in patients with schizophrenia.

MATERIALS AND METHODS

Subjects

The subjects were 10 Japanese schizophrenic inpatients (9 females and 1 male) who fulfilled the criteria for schizophrenia (undifferentiated type: 7 cases; paranoid type: 3 cases) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. The inclusion criteria were: 1) age between 18 to 40; 2) clinically stable; 3) treated with the same dosage of antipsychotics for at least 3 months; 4) physically healthy, without any history of substance abuse, neurological disorder, or delirium, and without any pituitary gland abnormalities on brain magnetic resonance imaging; 5) the presence of hyperprolactinemia; and 6) symptoms caused by hyperprolactinemia, such as oligomenorrhea, amenorrhea, or erectile dysfunction. Oligomenorrhea was defined as infrequent, irregularly timed episodes of menstrual bleeding occurring at intervals of more than 35 days from the previous menstrual cycle, and amenorrhea was defined as the absence of menstruation for more than six months or more than three menstrual cycles.

Methods

The study was an open-label trial of aripiprazole coadministration with causative drugs. Aripiprazole was started at 3 mg/day and titrated up to 18 mg/day at the clinician's discretion, as needed. The aripiprazole dose increment was determined at each physician's discretion because the fact that various antipsychotics with different doses had been administered to the subjects did not allow us to use a strict increment design. The doses of the other medications were fixed throughout the study period. No other medications that could affect prolactin concentrations were allowed. It has been shown that the plasma concentrations of both aripiprazole and its active metabolite, dehydroaripiprazole, reach a steady-state by 2 weeks in repeated oral administration [10]. Therefore, blood samples were taken the morning before the start of aripiprazole coadministration and then at least 2 weeks after the final fixed doses of aripiprazole. On the same day as the blood sampling time points, psychiatric symptom severity was evaluated by the Clinical Global Impression-Improvement (CGI-I) scale. Serum prolactin concentrations were measured using Immuno Enzymometric Assay (ST AIA-PACK PRL, TOSOH, Tokyo). Hyperprolactinemia was defined as a serum prolactin concentrations greater than 30 ng/ml for females and greater than 20 ng/ml for males. The study end point was decided by each physician so that the patients were enrolled in the study long enough to confirm whether the hyperprolactinemia-associated symptoms were improved by the addition of aripiprazole. This study was conducted in accordance with the Declaration of Helsinki, and all participants gave written informed consent.

Statistical analysis

The Wilcoxon signed-rank test was used for statistical analysis of the change in serum prolactin concentration before and after aripiprazole coadministration. A P value of 0.05 or less was regarded as statistically significant. SPSS 11.0 for Windows SPSS, Japan Inc., Tokyo was used for the statistical analysis.

Table 1. Clinical characteristics and course of 9 patients with antipsychotic-induced hyperprolactinemia before and after aripiprazole coadministration

Case	Sex	Age	PRL (ng/ml) Before	Associated symptoms	Causative drugs and doses (mg/day)	Aripiprazole dose (mg/day)	PRL (ng/ml) After	Time point of second PRL	Outcome
1	F	18	49.0	Amenorrhea	RIS 8	6	29.8	8 weeks	Cycle regularized
2	F	23	45.0	Oligomenorrhea	OLZ 5	6	19.7	4 weeks	Cycle regularized
3	F	33	56.1	Oligomenorrhea	RIS 2	6	15.3	14 weeks	Cycle regularized
4	F	24	125.2	Amenorrhea	HPD 15, ZTP 300	12	49.3	4 weeks	Menstruation regained
5	F	23	47.0	Oligomenorrhea	BPD 12, LPZ 25	6	19.2	4 weeks	unchanged
6	F	24	153.3	Oligomenorrhea	RIS 3, LPZ 15	6	53.0	10 weeks	unchanged
7	F	32	116.7	Oligomenorrhea	RIS 4, QTP 200	6	40.1	11 weeks	unchanged
8	F	34	110.1	Oligomenorrhea	RIS 8, LPZ 50	18	32.6	29 weeks	unchanged
9	M	40	27.3	Erectile dysfunction	RIS 3	3	9.8	30 weeks	Erection improved
Mean		27.9	81.1			7.7	29.9*	12.7 weeks	

Abbreviations: PRL: prolactin, RIS: risperidone, OLZ: olanzapine, HPD: haloperidol, ZTP: zotepine, BPD: bromperidol, LPZ: levomepromazine, QTP: quetiapine.

*p =0.008 compared with before coadministration

RESULTS

Patient characteristics

Table 1 shows the clinical characteristics of the 9 patients (8 females, 1 male) with anti-psychotic-induced hyperprolactinemia and associated side effects. One (1) female with oligomenorrhea dropped out because of insomnia during the coadministration of aripiprazole 6 mg/day. The mean age (range) was 27.9 (18-40) years old. Four (4) cases had been treated with antipsychotic monotherapy, and 5 cases had received two antipsychotic drugs. Six (6) of the females exhibited oligomenorrhea, the other 2 suffered from amenorrhea, and the male had erectile dysfunction. Aripiprazole was coadministered for more than 3 months. The mean dose (range) of aripiprazole was 7.7 (3-18) mg/day.

Clinical outcome

As shown in Table 1, the mean time point (range) at which prolactin concentrations were measured during aripiprazole coadministration was 12.2 (2-30) weeks after the final fixed doses of aripiprazole. The mean serum concentration (range) of prolactin of 29.9 (9.8-53.0) ng/ml during aripiprazole coadministration was significantly (p=0.008) lower than that before aripiprazole coadministration (81.1 (27.3-153.3) ng/ml). Two (2) females with oligomenorrhea and 1 female with amenorrhea exhibited normalized regular menstrual cycles, and 1 female with amenorrhea regained menstruation. The erectile dysfunction disappeared in the male. The associated symptoms did not improve in the other 4 females. Neither significant changes in the CGI-I scores nor apparent side effects were observed throughout the combination period (data are not shown). There were no statistical differences in terms of the chlorpromazine and risperidone equivalent doses [11, 12] between patients with and without improvement in the associated symptoms (data are not shown)

DISCUSSION

Previous studies [13-16] have shown that switching from prolactin-raising antipsychotics to aripiprazole is useful for treating antipsychotic-induced hyperprolactinemia in schizophrenic patients, with no significant changes in overall psychopathology. However, clinicians generally hesitate to change antipsychotic regimens, especially in clinically stable patients maintaining a high level of functioning, since such a strategy is sometimes accompanied by the risk that psychotic symptoms may worsen later. Actually, Mir et al. intended to demonstrate the efficacy of the switching strategy on antipsychotic-induced hyperprolactinemia at the start of the study [14]. However, they abandoned their plan to completely discontinue the causative drugs during the study because half of the patients attained subjective satisfaction with the combination of aripiprazole and their previous antipsychotic medications. Meanwhile, 3 [14-16] of 4 previous studies on switching to aripiprazole noted that the prolactin concentrations decreased during the combination period.

The present subjects might be heterogeneous, since 10 patients received 7 different types (or combinations thereof) of antipsychotics and 4 different doses of adjunctive aripiprazole. However, aripiprazole coadministration yielded consistent prolactin concentration profiles: all subjects exhibited decreased prolactin concentrations with significance. This result is consistent with a previous study [9] and case reports [17-21] showing the successful

treatment of antipsychotic-induced hyperprolactinemia by aripiprazole addition. However, more than 15 mg/day of aripiprazole was coadministered in all the studies mentioned above, and the incidences of adverse effects such as insomnia (42%), dry mouth (31%), and headache (23%) were not low in the systematic study by Shim et al [9]. A recent study [22] still treated hyperprolactinemia induced by risperidone with 10 mg/day of aripiprazole. In the present study, the mean 7.7 mg/day of aripiprazole was enough to decrease serum prolactin concentrations without any apparent side effects or worsening of clinical symptoms. Therefore, even smaller doses of coadministered aripiprazole may effectively limit excessive prolactin response without interfering with the benefits of existing prescriptions.

In this study, aripiprazole coadministration lowered serum prolactin concentrations in 5 patients who had received various combinations of two antipsychotics. This finding suggests that the add-on strategy is useful regardless of the causative drugs. However, it is noted that antipsychotic polypharmacy should not be permanently continued, and that the aripiprazole add-on strategy should be followed by switching.

On the other hand, the prolactin concentration was not completely normalized in 4 out of 9 cases, nor did the symptoms associated with hyperprolactinemia improve in all of the patients. These results imply that the impact of this strategy may be limited in subjects with excessively high prolactin concentrations. Nevertheless, the possibility that higher doses of aripiprazole might have normalized the prolactin concentrations in the 4 patients treated with 2 antipsychotic drugs cannot be entirely ruled out.

The time point at which prolactin concentrations were measured during aripiprazole coadministration differed among the subjects. This might not be a very satisfactory method, since the measurement of the prolactin concentration should have been at the end point of the study. However, it has been suggested that prolactin elevation by antipsychotics tends to be attenuated in long-term treatment [23]. Interestingly, in this study, administration for 4 weeks decreased the prolactin concentrations in 3 subjects. Therefore, it is possible that a more stringent study design might have resulted in aripiprazole having a more significant effect on the prolactin concentrations.

Aripiprazole has a high dopamine D2 receptor affinity, with about 30% of intrinsic activity of postsynaptic dopamine receptor [9]. In the presence of dopamine hypoactivity induced by antipsychotics, aripiprazole may act as a dopamine agonist, leading to decreases in prolactin concentrations.

This study has several limitations: first, it was an open-label study; second, the sample size was small; and third, the clinical symptoms and the side effects were not systematically evaluated by rating scales. An additional placebo-controlled study with a larger number of subjects should be performed to confirm the clinical usefulness of aripiprazole coadministration.

CONCLUSION

The present study suggests that even small doses of coadministered aripiprazole effectively limit excessive prolactin response to antipsychotics without interfering with the benefits of existing prescriptions.

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REFERENCES

[1] Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinemia, mechanisms, clinical features and management. Drugs 2004; 64: 2291-2314.

[2] Mihara K, Kondo T, Suzuki A, Yasui N, Nagashima U, Ono S, Otani K, Kaneko S. Prolactin response to nemonapride, a selective antagonist for D2 like dopamine receptors, in schizophrenic patients in relation to Taq1A polymorphism of DRD2 gene. Psychopharmacology 2000; 149: 246-250.

[3] Mihara K, Suzuki A, Kondo T, Yasui-Furukori N, Ono S, Otani K, Kaneko S, Inoue Y. Relationship between Taq1 A dopamine D2 receptor (DRD2) polymorphism and prolactin response to bromperidol. Am J Med Genet 2001; 105: 271-274.

[4] Harvey PW, Everett DJ, Springall CJ. Adverse effects of prolactin in rodents and humans: breast and prostate cancer. J Psychopharmacol 22 suppl 2008; 2: S20-S27.

[5] O'Keane V. Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia. J Psychopharmacol 22 suppl 2008; 2: S70-S75.
[6] Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, MailmanR. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28: 1400-1411.
[7] Harrison TS, Perry CM. Aripiprazole; a review of its use in schizophrenia and schizoaffective disorder. Drugs 2004; 64: 1715-1736.
[8] Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, Ali MW. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002; 63: 763-771.
[9] Shim JC, Shin JGK, Kelly DL, Jung DU, Seo YS, Liu KH, Shon JH, Conley RR. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry 2007; 164: 1404-1410.
[10] Kubo M, Koue T, Maune H, Fukuda T, Azuma J. Pharmacokinetics of aripiprazole, a new antipsychotic, following oral dosing in healthy adult Japanese volunteers: influence of CYP2D6 polymorphism. Drug Metab Pharmacokinet 2007; 22: 358-366.
[11] Inagaki A, Inada T, Fujii Y, Yagi G. Dose equivalence of psychotropic drugs. Part II. Dose equivalence of orally administered neuroleptics. Jpn J Clin Psychopharmacol 1998; 1: 215-219.
[12] Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003; 64: 663-667.
[13] Lee BH, Kim YK, Park SH. Using aripiprazole to resolve antipsychotic-induced symptomatic hyperprolactinemia: a pilot study. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30: 714-717.
[14] Mir A, Shivakumar K, Williamson RJ, McAllister V, O'Keane V, Aitchison KJ. Change in sexual dysfunction with aripiprazole: a switching or add-on study. J Psychopharmacol 2008; 22: 244-253.
[15] Lu ML, Shen WW, Chen CH. Time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 1978-1981.
[16] Byerly MJ, Marcus RN, Tran QV, Eudicone JM, Whitehead R, Baker RA. Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: analysis of a randomized, open-label study. Schizophr Res 2009; 107: 218-222.
[17] Wahl R, Ostroff R. Reversal of symptomatic hyperprolactinemia by aripiprazole. Am J Psychiatry 2005; 162: 1542-1543.
[18] Lin SK, Chen CK. Reversal of antipsychotic-induced hyperprolactinemia, weight gain, and dyslipidemia by aripiprazole: a case report. J Clin Psychiatry 2006; 67: 1307.
[19] Lorenz RA, Weinstein B. Resolution of haloperidol-induced hyperprolactinemia with aripiprazole. J Clin Psychopharmacol 2007; 27: 524-525.
[20] Wolf J, Fielder U. Hyperprolactinemia and amenorrhea associated with olanzapine normalized after addition of aripiprazole. J Clin Pharmacol Ther 2007; 32: 197-198.
[21] Rainka MM, Capote HA, Ross CA, Gengo FM. Attenuation of risperidone-induced hyperprolactinemia with the addition of aripiprazole. J Clin Pharmacol Ther 2009; 34: 595-598.
[22] Chen JX, Su YA, Wang SL, Bian QT, Liu YH, Wang N, Yang FD, Haile C, Kosten TR, Zhang XYZ. Aripiprazole treatment of risperidone-induced hyperprolactinemia. J Clin Psychiatry 2009; 70:1058-1059.
[23] Sawamura K, Suzuki Y, Fukui N, Sugai T, Someya T. Gender differences in prolactin elevation induced by olanzapine in Japanese drug-naïve schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30: 1511-1514.