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Time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole

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ABSTRACT

Hyperprolactinemia is an important but neglected adverse effect of antipsychotic medication. All first generation antipsychotics and the second generation antipsychotics amisulpride and risperidone have been shown to cause marked elevation in serum prolactin levels, whereas most other second generation antipsychotics and aripiprazole appear to have little or no effect on serum prolactin levels. This study was aimed to assess the time course of changes in antipsychotic-induced hyperprolactinemia during the process of antipsychotic switching to aripiprazole. Twenty-three female schizophrenic subjects with risperidone- or sulpiride-induced symptomatic hyperprolactinemia were recruited into the study and 20 of them completed the trial. We added aripiprazole to the therapeutic dose first, then overlapped the preexisting antipsychotic treatment and aripiprazole, and finally tapered the preexisting antipsychotic treatment. Clinical status was assessed by using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Severity Scale (CGI-S). Assessment scales and serum prolactin levels were measured at baseline, during the combination treatment period, and four weeks after having completed discontinuation of the preexisting antipsychotic treatment. Switching antipsychotic drugs to aripiprazole was effective in reducing serum prolactin levels and restoring menstruation in schizophrenic patients who received prolactin-raising antipsychotics. Mean serum prolactin levels at baseline, during combination period, and after the switch were 97.0±69.0 ng/ml, 27.2±10.6 ng/ml ($p<0.001$, vs. baseline), and 12.2±5.3 ng/ml ($p<0.001$, vs. baseline), respectively. None of the study subjects experienced any serious adverse effects during the switching process. No significant changes were noted in the PANSS and CGI-S scores during the switching process. The prolactin-normalizing effects of aripiprazole are likely caused by the unique characteristics of the dopamine partial agonist with its high affinity for dopamine D_2 receptors.

1. Introduction

Antipsychotic drugs are medications used to treat schizophrenia and other psychotic disorders. All current antipsychotic drugs have the ability to block dopamine D_2 receptors (Kapur and Mamo, 2003). The antipsychotic effect is thought to act on the dopaminergic neurons of the mesolimbic system which are linked with psychotic symptoms. However, antipsychotic drugs can cause unwanted side effects which are related to dopamine D_2 blockade in non-mesolimbic regions. Among these, hyperprolactinemia is an important but neglected adverse effect (Haddad and Wieck, 2004; Byerly et al., 2007).

Antipsychotic drugs block dopamine D_2 receptors on lactotroph cells in the anterior pituitary gland and thus remove the inhibitory influence on prolactin secretion (Wieck and Haddad, 2003). Several studies have shown that first generation antipsychotic treatment with therapeutic dosages can increase mean prolactin levels up to ten-fold (Meltzer and Fang, 1976; Gruen et al., 1978; Kuruvilla et al., 1992; Bushe and Shaw, 2007). Partial tolerance may occur during chronic antipsychotic treatment (Brown and Laughren, 1981) although patients who have been treated for several years still have significantly higher prolactin levels than healthy controls (Rivera et al., 1976). The second generation antipsychotic drugs (SGAs) are generally defined as drugs that cause minimal extrapyramidal symptoms and prolactin elevation at therapeutic dosages. However, amisulpride and risperidone both cause a marked increase in prolactin levels (Baptista et al., 1997; Kleinberg et al., 1999; Haddad and Wieck, 2004).

Aripiprazole is a potent partial agonist (i.e., exerting both agonistic and antagonistic effects on receptors) at D_2 and 5-HT_{1A} receptors, and has potent antagonistic activity at 5-HT_{2A} receptors (Jordan et al.,

Abbreviations: CGI-S, Clinical Global Impression Severity Scale; PANSS, Positive and Negative Syndrome Scale; SGA, second generation antipsychotic drug.

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2002; Hirose et al., 2004). In contrast to some SGAs, aripiprazole is associated with minimal weight gain and has minimal negative impact on metabolic and neuroendocrine parameters (Casey et al., 2003; Naber and Lambert, 2004). The effects of substituting aripiprazole for other antipsychotic agents on schizophrenic patients with antipsychotic-induced hyperprolactinemia have been proven in several studies (Casey et al., 2003; Lin and Chen, 2006). Some case reports have shown the reversal of antipsychotic-induced hyperprolactinemia after addition of aripiprazole (Wahl and Ostroff, 2005; Lin and Chen, 2006; Wolf and Fiedler, 2007; Chen et al., 2008; Mir et al., 2008). Recently, Shim et al. (2007) conducted a randomized, double-blind, placebo-controlled study and showed that adjunctive aripiprazole treatment improved haloperidol-induced hyperprolactinemia in both sexes with no significant effects on psychopathology or extrapyramidal symptoms. Contrary to these findings, Paulzen and Gründer (2007) reported a lack of an expected decrease of serum prolactin levels by adding aripiprazole in patients treated with amisulpride.

With the high affinity for dopamine D_2 receptors, sulpiride and risperidone have a strong association with hyperprolactinemia (Baptista et al., 1997; Kleinberg et al., 1999). To assess the effectiveness and time course of aripiprazole on the antipsychotic-induced hyperprolactinemia during the process of switching, we conducted an open-label trial of aripiprazole as a replacement for risperidone or sulpiride in female schizophrenic patients who were suffering from symptomatic hyperprolactinemia.

2. Methods

2.1. Study subjects

The open-label study was approved by the facility's institutional review board. The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2000). After giving a description of the study to the patients, we obtained written informed consent from the participants. The inclusion criteria of recruited patients were (1) 18 to 50 year-old women, (2) to have a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and having taken a stabilized dose of risperidone or sulpiride for at least three months with a stable psychiatric condition, (3) to have symptomatic antipsychotic-induced hyperprolactinemia, such as oligomenorrhea, amenorrhea, and galactorrhea. Oligomenorrhea was defined as infrequent, irregularly timed episodes of menstrual bleeding occurring at intervals of more than 35 days from the previous menstrual cycle. Amenorrhea was defined as the absence of menstruation for more than six months or more than three menstrual cycles, after prior establishment of regular periods. Galactorrhea was defined as the spontaneous flow of milk from the breast, unassociated with childbirth or nursing. Patients with known endocrine disease, gynecological problems, or other major medical illnesses were excluded.

2.2. Study design

The study was an open-label trial of aripiprazole as a replacement for risperidone or sulpiride. The first blood sampling was obtained before the initiation of aripiprazole. The switching strategy was the delayed withdrawal of the preexisting antipsychotic medication followed by addition of the new antipsychotic agent at a therapeutic dosage (Weiden, 2006). Aripiprazole was started at 10 mg/day and could be increased to 30 mg/day at the clinician's discretion. After achieving the therapeutic dosage of aripiprazole, subjects were maintained at the combination treatment for four weeks and then received a second blood sampling. After the second blood sampling, the doses of preexisting antipsychotic drugs were immediately decreased by risperidone 1.5 mg/day or sulpiride 200 mg/day. Then we gradually tapered them at the rate of risperidone 1.5 mg/day or sulpiride 200 mg/day per four weeks. The mean of the time to complete discontinuation of preexisting antipsychotic drugs was 7.6±3.9 weeks. The third blood sampling was obtained four weeks following the complete discontinuation of preexisting antipsychotic drugs. Benzodiazepine, as needed for anxiety or insomnia, and anticholinergic agents, as needed for extrapyramidal symptoms, were allowed. The subjects could not receive any other medications that could alter serum prolactin levels during the switching period. Compliance was monitored by pill counts and by participant's reports.

We assessed the subjects for treatment efficacy with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impression Severity Scale (CGI-S) (Guy, 1976) at baseline, during the combination treatment period, and four weeks after complete discontinuation of the preexisting antipsychotic medication. The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987) was used biweekly for monitoring both extrapyramidal symptoms and other side-effects. A single rater performed all assessments throughout the trial.

Blood samples were obtained in the morning after an overnight fast at baseline, during the combination treatment, and four weeks after complete discontinuation of risperidone or sulpiride. Prolactin was measured in the chemistry laboratory of the Taipei Institute of Pathology using electrochemiluminescence immunoassays, with commercial kits for measuring prolactin (Elecsys 2010 immunoassay analyzers, Boehringer Mannhein, Indianapolis, USA). Hyperprolactinemia was defined as a serum prolactin level being greater than 25 ng/ml for women.

2.3. Statistical analysis

We presented the data as percentages and mean values±SD unless otherwise indicated. Data were analyzed using repeated-measures analysis of variance (ANOVA), followed by a post hoc paired Student's *t*-test. The differences were considered significant if *p* values were less than 0.05.

3. Results

Twenty-three subjects consented to participate. Two subjects discontinued the medication by themselves due to adverse effects (sleep disturbance and excessive anxiety) and one subject was lost to follow-up. The remaining twenty subjects completed the study and their data are reported in the following results.

All subjects were Taiwanese women who had mean±SD age of 31.7±9.3 years. The mean duration of illness was 5.5±5.4 years. The mean duration of receiving preexisting antipsychotic medication was 16.8±13.4 months. Twelve subjects had been taking risperidone (mean±SD dose of 4.8±1.5 mg/day) and eight subjects had been taking sulpiride (mean±SD dose of 500.0±151.2 mg/day). Table 1 lists the clinical characteristics of 20 study subjects.

At baseline, all subjects were experiencing menstrual disturbance (eleven subjects with oligomenorrhea and nine subjects with amenorrhea). Three subjects were also experiencing galactorrhea at baseline. The serum prolactin levels differed significantly among the three blood samplings ($F=36.08$, $df=2$, $p<0.001$). Mean serum prolactin levels at baseline, during the combination period, and after the switch were 97.0±69.0 ng/ml, 27.2±10.6 ng/ml ($p<0.001$, vs. baseline), and 12.2±5.3 ng/ml ($p<0.001$, vs. baseline), respectively. During the period of combination treatment, seven subjects had normalized serum prolactin levels and 14 subjects reported having regular menstrual cycles. After the switch to aripiprazole, all subjects reported having regular menstrual cycles and their serum prolactin levels were all within normal range.

Overall, no significant changes were noted in the PANSS and CGI-S scores during the switching process. Mean total PANSS scores were 53.4±7.4, 52.2±7.7, and 54.0±9.8 at baseline, during the combination

Table 1
The clinical characteristics of 20 study subjects

Patient number	Age, years	Hyperprolactinemia symptoms	Preexisting antipsychotics	Aripiprazole dosage (mg/day)	Baseline			During cross-over			After cross-over		
					Prolactin (ng/ml)	PANSS	CGI-S	Prolactin (ng/ml)	PANSS	CGI-S	Prolactin (ng/ml)	PANSS	CGI-S
1	20	Amenorrhea, Galactorrhea	Sulpiride 400 mg	10	107.0	45	3	32.7	44	3	17.0	45	3
2	37	Oligomenorrhea	Risperidone 6 mg	20	66.9	51	3	33.2	52	3	11.3	50	3
3	28	Oligomenorrhea	Risperidone 6 mg	20	78.4	53	3	6.1	55	3	6.3	50	3
4	30	Amenorrhea, Galactorrhea	Sulpiride 800 mg	20	98.6	45	3	25.2	40	3	13.7	42	3
5	18	Amenorrhea	Risperidone 6 mg	30	89.2	62	4	22.8	60	4	13.0	63	4
6	39	Amenorrhea, Galactorrhea	Risperidone 3 mg	20	122.1	40	3	37.2	42	3	18.2	45	3
7	26	Amenorrhea	Sulpiride 400 mg	10	91.8	42	3	20.7	40	3	8.9	43	3
8	31	Amenorrhea	Risperidone 4.5 mg	20	81.6	55	3	32.8	50	3	18.2	52	3
9	35	Oligomenorrhea	Sulpiride 600 mg	20	59.6	50	3	27.1	48	3	8.6	52	3
10	41	Amenorrhea	Risperidone 4.5 mg	20	102.8	48	3	41.0	45	3	21.8	46	3
11	27	Amenorrhea	Sulpiride 600 mg	20	88.1	56	3	32.6	50	3	12.5	51	3
12	33	Oligomenorrhea	Risperidone 6 mg	30	64.9	65	4	28.4	62	4	14.8	71	4
13	19	Oligomenorrhea	Risperidone 1.5 mg	10	82.5	58	4	5.25	56	3	2.06	54	3
14	44	Amenorrhea	Risperidone 4.5 mg	20	377.6	60	4	44.8	62	4	14.6	62	4
15	19	Oligomenorrhea	Sulpiride 400 mg	20	107.3	56	3	32.5	54	3	2.61	56	3
16	48	Oligomenorrhea	Risperidone 3 mg	20	43.3	58	4	12.8	56	3	6.9	52	3
17	29	Oligomenorrhea	Risperidone 6 mg	20	87.7	64	4	36.2	66	4	17.3	72	4
18	39	Oligomenorrhea	Risperidone 6 mg	20	70.8	62	4	17.5	60	4	8.9	74	4
19	46	Oligomenorrhea	Sulpiride 400 mg	10	63.5	52	3	31.2	54	3	15.4	56	3
20	24	Oligomenorrhea	Sulpiride 400 mg	10	55.6	46	3	24.6	48	3	12.8	44	3

period, and after the switch, respectively. Mean CGI-S scores were 3.4±0.5, 3.3±0.4, and 3.3±0.4 at baseline, during the combination period, and after the switch, respectively.

The mean±SD dose of aripiprazole was 18.5±5.9 mg/day. Although many subjects reported one or more adverse effects during the trial, most were mild to moderate in intensity. The most frequently reported adverse effects were reduced duration of sleep (n=10), tension (n=8), nausea (n=6), akathisia (n=5), and tremor (n=4).

4. Discussion

To the best of our knowledge, this is the first study to assess the time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole. The present study showed that aripiprazole could attenuate the antipsychotic-induced hyperprolactinemia during the combination period and successfully reverse it following the medication switch without serious side effects or sacrificing psychopathology.

With the high affinity for dopamine D_2 receptors, sulpiride and risperidone have a strong association with hyperprolactinemia (Baptista et al., 1997; Kleinberg et al., 1999). Although both the extrapyramidal side effects and hyperprolactinemia have been related to dopamine D_2 receptor blockade, different pathways are involved. The motor side effects of antipsychotics are associated with the blockade of striatal dopamine D_2 receptors, whereas prolactin elevation is associated with the blockade of dopamine D_2 receptors on anterior pituitary lactotrophs. Natesan et al. (2006) reported that risperidone and haloperidol showed dose and striatal dopamine D_2 receptor occupancy dependent prolactin elevations. A 250% increase in prolactin levels from baseline corresponds to 27% dopamine striatal dopamine D_2 receptor occupancy for risperidone, while for haloperidol it corresponds to 80% dopamine striatal dopamine D_2 receptor occupancy (Natesan et al., 2006). One possible explanation is that sulpiride and risperidone have poor blood-brain barrier penetration properties (Mauri et al., 1996; Kapur and Remington, 2001). The relative difficulty to get across the blood-brain barrier is important with respect to the effect on prolactin elevation. The desired central dopamine receptor occupancy should be achieved at higher doses, which would result in a greater number of peripheral D_2 receptors being blocked in the pituitary (Kapur et al., 2002). The pituitary lies outside the blood-brain barrier and is accessible to drugs that find it hard to cross the blood-brain barrier. As a result of the differences in hydrophilic or lipophilic properties of antipsychotic agents, different penetration properties across the blood-brain barrier might account for the differential effects on serum prolactin levels (Kapur and Remington, 2001; Kapur et al., 2002).

Aripiprazole acts as a functional antagonist at dopamine D_2 receptors under hyperdopaminergic conditions but exhibits functional agonist properties under hypodopaminergic conditions (Shapiro et al., 2003). Compared to risperidone and sulpiride, aripiprazole has a higher affinity to the dopamine receptor and acts as a partial dopamine agonist (Kuroki et al., 1999; Shapiro et al., 2003). When aripiprazole is co-administered with risperidone or sulpiride, it may bind to the dopamine receptor more robustly and acts as a dopamine receptor agonist in an antipsychotic-induced hypodopaminergic state.

Because of these unique pharmacological profiles, aripiprazole monotherapy may lower serum prolactin levels in subjects with prior antipsychotic exposure (Casey et al., 2003; Marder et al., 2003). In the present study, all subjects reported that they had regular menstrual cycles and their serum prolactin levels were all within normal range after switching to aripiprazole.

No serious adverse effects were noted in the study. Overall, the switching process was smooth and well-tolerated by the subjects. Some patients experienced insomnia, tension, and extrapyramidal symptoms. However, these adverse effects were mild to moderate in intensity.

Previous studies have showed the effectiveness of aripiprazole for treating positive and negative symptoms, as well as a safe and tolerable adverse effect profile for both initiating treatment and switching from other antipsychotic agents in schizophrenic patients (Kane et al., 2002; Casey et al., 2003; Marder et al., 2003). In the present study, adjunctive aripiprazole to preexisting antipsychotic treatment and then switching to aripiprazole monotherapy did not produce significant changes in psychopathology as measured by PANSS and CGI-S. No further improvement in PANSS and CGI-S scores can be associated with the characteristics of our subjects who were in a clinically stable state.

Several limitations of our study should be considered. First, it was an open-label study, and this study design was subject to the placebo effect. However, based on the pattern of sustained changes in serum prolactin levels, we suggest that these changes were not solely due to the placebo effect. Second, the duration of aripiprazole therapy in the study was relatively short. We cannot be sure that the stable psychopathology would persist in a longer follow-up period. Third,

the small sample size, all female subjects, and absence of other antipsychotic-treated subjects may limit the interpretation and generalizability of our findings. Fourth, brain imaging studies were not performed as part of the study enrollment to rule out pituitary tumors that may confound the prolactin results. Nonetheless, extremely high prolactin levels should warrant an investigation into other causes such as prolactinoma. Therefore, studies that include larger samples receiving different antipsychotics, longer treatment duration, and more comprehensive assessment will help to ascertain the role of aripiprazole in antipsychotic-induced hyperprolactinemia.

5. Conclusions

The clinical implications of our study are that antipsychotic-induced hyperprolactinemia could be partially normalized after adding aripiprazole and completely reversed after switching to aripiprazole. Aripiprazole has a high affinity to dopamine D_2 receptors and has the unique characteristic of being a partial dopamine D_2 agonist, which are likely to explain the phenomena observed in this study.

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