Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 537–540

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Gender-specific prolactin response to antipsychotic treatments with risperidone and olanzapine and its relationship to drug concentrations in patients with acutely exacerbated schizophrenia

Norio Yasui-Furukori [a,*], Manabu Saito [a], Taku Nakagami [a,b], Norio Sugawara [a,c], Yasushi Sato [a,c], Shoko Tsuchimine [a], Hanako Furukori [d], Sunao Kaneko [a]

[a] Department of Neuropsychiatry, Graduate School of Medicine, Hirosaki University, Hirosaki 036-8562, Japan
[b] Department of Psychiatry, Hirosaki-Aiseikai Hospital, Hirosaki Japan
[c] Department of Psychiatry, Ohdate City Hospital, Ohdate, Japan
[d] Department of Psychiatry, Kuroishi-Akebono Hospital, Kuroishi, Japan

ARTICLE INFO

Article history:
Received 7 October 2009
Received in revised form 26 January 2010
Accepted 11 February 2010
Available online 17 February 2010

Keywords:
Gender
Olanzapine
Prolactin
Risperidone

ABSTRACT

Hyperprolactinemia is a frequent consequence of treatment with antipsychotic agents, partially because the prolactin response to antipsychotics is related to dopamine blockade. Recent studies have suggested that the prolactin response to olanzapine is weaker than that to risperidone. Thus, we studied the effects of various factors on the elevated plasma prolactin levels caused by these medications. The subjects were 94 patients with acutely exacerbated schizophrenia (46 males, 48 females). For four weeks, they received 6 mg of risperidone and 20 mg of olanzapine daily. Plasma samples were collected before the medications were given and 12 h after the bedtime dosing each week. Treatment with either risperidone or olanzapine boosted plasma prolactin levels above baseline in both males and females. Prolactin levels were significantly higher in females than in males at all sampling points in both treatments. Risperidone increased prolactin significantly more than did olanzapine in both males and females. Delta prolactin (prolactin level at four weeks minus the baseline prolactin level) during olanzapine treatment significantly correlated with olanzapine concentration at 4th week ($r=-0.518$, $p<0.01$) only in males. Multiple regression analyses showed that delta prolactin during risperidone was significantly correlated with gender ($p<0.001$) and age ($p<0.05$) and that delta prolactin during olanzapine significantly correlated with gender ($p<0.001$) and drug concentration ($p<0.01$). The present study suggests that the predominant factors influencing hyperprolactinemia are young female for risperidone treatment, and being female and lower drug concentration as a predictor for hyperprolactinemia under olanzapine.

1. Introduction

Hyperprolactinemia has been assumed to be a frequent consequence of treatment with antipsychotic agents (Rubin, 1987; Petty, 1999). The major effects of hyperprolactinemia in women are amenorrhea, galactorrhea, cessation of normal cyclic ovarian function, loss of libido, occasional hirsutism (Rubin, 1987; Petty, 1999) and long-term risk of osteoporosis (Meaney et al., 2004). The effects in men include impotence, loss of libido, hypospermatogenesis (Rubin, 1987; Petty, 1999) and long-term risk of low bone density (Meaney et al., 2004).

Every antipsychotic has a different prolactin response. Risperidone has one of the highest propensities to elevate plasma prolactin levels (Kleinberg et al., 1999). Mean prolactin levels at a dose of 3 mg of risperidone are significantly higher than those in response to olanzapine or clozapine in males (Turrone et al., 2002). The elevation of prolactin induced by olanzapine is regarded as transient and mild compared to that induced by other antipsychotics such as haloperidol and risperidone that cause acute and persistent elevation of prolactin (Kinon et al., 2003). However, the prolactin response to neuroleptic treatments weakens over time (Sawamura et al., 2006).

Numerous studies have tried to identify specific factors influencing the prolactin response to neuroleptic treatments. Several studies have shown higher prolactin concentrations in females being treated with chlorpromazine (Meltzer et al., 1983; Harnryd et al., 1984), sulpiride (Harnryd et al., 1984), haloperidol (Linkowski et al., 1984; Yasui-Furukori et al., 2001), bromperidol (Yasui et al., 1998), nemonaprode (Otani et al., 1997), olanzapine (Sawamura et al., 2006) or risperidone (Yasui-Furukori et al., 2007; Yasui-Furukori et al., 2008). Several studies have suggested no association between plasma concentration of prolactin and age (Otani et al., 1993; Otani et al., 1997), whereas other studies have revealed that age is negatively correlated with

Abbreviations: PET, Positron emission tomography; DRD2, Dopamine D2 receptor.

* Corresponding author. Department of Neuropsychiatry, Hirosaki University School of Medicine, Hirosaki 036-8562, Japan. Tel.: +81 172 39 5352; fax: +81 172 39 5352.
E-mail address: yasufuru@cc.hirosaki-u.ac.jp (N. Yasui-Furukori).

0278-5846/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2010.02.014

plasma prolactin concentration in females (Yasui-Furukori et al., 2007; Yasui-Furukori et al., 2008).

In addition, several of our studies have indicated a significant association between plasma drug concentration and prolactin response to bromperidol (Yasui et al., 1998). On the other hand, cross-sectional studies revealed that prolactin concentrations are not correlated with plasma drug concentration of haloperidol (Yasui-Furukori et al., 2001) and risperidone (Yasui-Furukori et al., 2007; Yasui-Furukori et al., 2008) in females. A plausible explanation for this discrepancy is probably related to the cross-sectional study design, as baseline prolactin concentrations vary among individuals (particularly females). Therefore, prolactin response as measured by delta prolactin concentration is informative for clarifying the effects of various factors on hyperprolactinemia.

There is little information on how the two neuroleptic treatments risperidone and olanzapine differ with respect to prolactin response except a more recent study in children and adolescents (Migliardi et al., 2009). Therefore, prolactin responses to risperidone and olanzapine were compared in males and females with acutely exacerbated schizophrenia. In addition, the effect of drug concentration was also examined.

2. Methods

2.1. Subjects

The subjects consisted of 120 physically healthy inpatients who met the criteria for acute exacerbation of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Version IV-TR. They had not received any dopamine antagonists or other antipsychotic agents for at least four weeks. The study protocol was approved by the Ethics Committee of Graduate School of Medicine, Hirosaki University, and all patients gave their written informed consent to participate in the study.

2.2. Protocol

One hundred and twenty patients were randomly allocated into risperidone group and olanzapine group. Out of 120 patients, 94 (46 male and 48 female) patients completed the protocol, while 26 patients were withdrawn from this study because of moderate to severe side effects and proposal of withdrawal from this study before an endpoint. Three mg of risperidone was given twice daily (8 am and 8 pm) to 44 (22 male and 22 female) patients for four weeks. Ten mg of olanzapine was given twice daily (8 am and 8 pm) to 50 patients (24 males and 26 females) for four weeks. Means and SDs of age and body weight are given in Table 1. No other drugs were given, except biperiden 4–6 mg to 40 patients, flunitrazepam 1–4 mg to 68 patients and sennoside 12–48 mg to 32 patients. No depot antipsychotics were performed before. No female patients receiving hormonal therapy were enrolled in the study. For olanzapine and risperidone groups, 16 and 14 patients were premenopausal and 8 and 7 patients were postmenopausal, respectively, and the remaining was not available because of hysterectomy.

Blood samples for quantification of prolactin were obtained just before the 8 am dose was administered at 1, 2, 3 and 4 weeks of the medication and those of drug concentration were obtained at 4 weeks of the medication.

Table 1
Characteristics of patients treated with risperidone and olanzapine.

	Risperidone		Olanzapine	
	Males ($n=22$)	Females ($n=22$)	Males ($n=24$)	Females ($n=26$)
Age (years)	41.7 ± 7.6	43.6 ± 15.1	42.1 ± 14.2	42.2 ± 13.8
Body weight (kg)	66.4 ± 5.6	52.3 ± 6.8	67.7 ± 11.6	57.0 ± 11.4
Baseline prolactin level (ng/ml)	10.6 ± 4.9	14.3 ± 7.8	11.3 ± 6.7	13.8 ± 8.3
Prolactin level at 1 weeks (ng/ml)	47.2 ± 11.0	147.9 ± 64.4	22.3 ± 10.8	56.9 ± 38.1
Prolactin level at 2 weeks (ng/ml)	53.0 ± 16.0	173.6 ± 65.3	34.3 ± 21.6	75.8 ± 38.0
Prolactin level at 3 weeks (ng/ml)	51.6 ± 13.8	171.3 ± 65.3	38.1 ± 21.1	87.4 ± 42.2
Prolactin level at 4 weeks (ng/ml)	53.6 ± 12.9	170.4 ± 76.9	34.1 ± 20.3	68.8 ± 34.0
Drug concentration at 4 weeks (ng/ml)	37.0 ± 12.3	53.2 ± 35.7	10.0 ± 4.7	12.5 ± 7.0

Data shows mean ± SD.

2.3. Assay

Plasma concentrations of risperidone and 9-hydroxyrisperidone were determined by the LC–MS–MS method as described before (Nakagami et al., 2005; Yasui-Furukori et al., 2007; Yasui-Furukori et al., 2008). The limits of quantifications were 0.3 ng/ml, and intra- and inter-assay CV values were less than 5% at 0.3 ng/ml of both compounds. Plasma concentrations of olanzapine were determined by the HPLC method (D'Arrigo et al., 2006). The limits of quantifications were 2.5 ng/ml, and intra- and inter-assay CV values were less than 10% at 5 ng/ml of olanzapine.

Plasma prolactin concentrations were measured by enzyme immunoassay (IMX Prolactin Dinapack, Dainabot Ltd., Tokyo, Japan). The limit of detection of prolactin was 1.0 ng/ml, and intra- and inter-assay CV values were less than 5.6% at plasma concentrations of 8.0, 20.0 and 40.0 ng/ml.

2.4. Statistical analysis

Delta prolactin was defined as prolactin level at four weeks minus the baseline prolactin level. Effect sizes were described as Cohen's d values. The time comparison of prolactin concentration was performed with repeated measurement ANOVA followed by Bonferroni's correction. Gender and drug differences in prolactin concentration were analyzed using t-tests followed by Bonferroni's correction. Simple (Pearson) correlation tests were used to examine the relationship between prolactin concentration and drug concentrations. Active moiety concentration (risperidone plus 9-hydroxyrisperidone) was used as drug concentration for risperidone treatment because the pharmacological profile of 9-hydroxyrisperidone is similar to risperidone. Multiple regression analyses were performed in order to examine the relationship between prolactin concentration and age, body weight, smoking status, drug concentration and gender. Dummy variables were used for analyses of gender, smoking and drug effects as follows: male = 0, female = 1 and nonsmoking = 0, smoking = 1. A p value of less than 0.05 was regarded as statistically significant. All analyses were performed using SPSS 15.0J for Windows (SPSS Japan Inc., Tokyo, Japan).

3. Results

Plasma prolactin concentrations over time are shown in Fig. 1. Plasma prolactin concentrations were significantly elevated for males and females at one ($t=13.907$, df = 21, $p<0.001$, Cohen's $d=4.22$ and $t=10.387$, $p<0.001$, Cohen's $d=2.93$), two ($t=12.113$, df = 21, $p<0.001$, Cohen's $d=3.49$ and $t=10.091$, df = 21, $p<0.001$, Cohen's $d=2.90$), three ($t=13.514$, df = 21, $p<0.001$, Cohen's $d=3.43$ and $t=11.706$, df = 21, $p<0.001$, Cohen's $d=3.30$) and four weeks ($t=13.028$, df = 21, $p<0.001$ Cohen's $d=3.90$ and $t=9.933$, df = 21, $p<0.001$, Cohen's $d=2.86$) after initiation of risperidone treatment. Plasma prolactin concentrations in females during risperidone were significantly higher than in males at one ($t=7.274$, df = 42, $p<0.001$, Cohen's $d=2.23$), two ($t=7.151$, df = 42, $p<0.001$, Cohen's $d=2.21$), three ($t=8.216$, df = 42, $p<0.001$, Cohen's $d=2.53$) and four weeks ($t=6.939$, df = 42, $p<0.001$, Cohen's $d=2.14$). Olanzapine treatment induced high plasma concentrations of prolactin in