Rapid Leptin Elevation after Initiation of Olanzapine?

Hsuan-Chi Wang^a Po See Chen^{a, b} I Hui Lee^{a, b} Yen Kuang Yang^{a, b}
Tzung Lih Yeh^{a, b} Ru-Band Lu^{a, b, c}

^aDepartment of Psychiatry, National Cheng Kung University Hospital, ^bDepartment of Psychiatry and

^cInstitute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC

Key Words

Leptin • Weight gain • Olanzapine • Schizophrenia

Abstract

Weight gain is a common adverse effect associated with olanzapine treatment. Another side effect of olanzapine treatment is a significant increase in circulating leptin levels. This preliminary study monitored the changes in leptin levels for 2 weeks after olanzapine treatment had been initiated. The relationship between the changes in circulating leptin levels and alterations in body weight in 9 patients with schizophrenia who received olanzapine was examined. The results showed that olanzapine may cause a surge in circulating leptin levels before weight gain is manifested. Moreover, higher pretreatment circulating leptin levels predicted lower weight gains after olanzapine treatments ($r = -0.93$; $p < 0.05$) after controlling for the effect of sex.

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Introduction

Olanzapine, an atypical antipsychotic drug, has been shown to be effective in treating the positive and negative symptoms of schizophrenia with minimal extrapyrami-

dal side effects [1]. However, weight gain is a common and potentially serious complication of olanzapine treatment [2]. Olanzapine is also noted to be associated with new-onset glucose intolerance, diabetes and ketoacidosis [3–7]. The mechanisms and predictors of weight gain caused by olanzapine have become important clinical considerations.

Leptin is known as a hormone involved in weight regulation [8–11]. Circulating leptin reports the state of fat store to the hypothalamus. The neuroendocrine systems then adapt their functions to the current status of energy homeostasis and fat stores [12, 13]. During olanzapine treatment, leptin regulation may be altered [5, 14]. Previous studies have reported an association between olanzapine-induced weight gains and the elevation in serum leptin levels [15–17]. Melkersson and Hulting [14] and Wetterling [18] suggested that the influence of olanzapine on leptin levels may be related to its ability to induce weight gain.

While most previous studies have focused on serum leptin levels after olanzapine-induced weight gains occurred [14, 17–20], this preliminary study focused on the changes in serum leptin levels shortly after olanzapine initiation. Serum leptin levels and body weights of schizophrenic patients during the first 14 days of olanzapine treatment were obtained and analyzed.

Table 1. Demographic data and initial treatment profile

No.	Age years	Sex	BW kg	BMI	Olan- zapine mg	Propranolol mg (initiation time)	Plasma leptin levels, ng/ml		PANSS
							baseline (collection time)	4 h after first dose	
1	21	M	63	22.5	20	10 (0 h)	3.93 (17:30)	6.59	158
2	29	F	46	17.5	10	none	11.62 (06:30)	19.22	110
3	40	F	59	28.1	10	10 (day 11)	53.84 (12:00)	80.14	105
4	34	M	51	17.6	20	20 (0 h)	1.51 (12:50)	4.94	119
5	32	F	59	22.2	10	none	15.39 (10:00)	16.40	68
6	44	M	72	25.2	10	10 (0 h)	16.5 (07:00)	16.98	102
7	47	M	83	28.4	20	10 (17 h)	5.31 (16:25)	17.87	142
8	20	F	59	25.2	20	10 (0 h)	22.98 (19:00)	32.29	106
9	45	M	64	20.7	20	20 (16 h)	<0.01 (17:00)	0.87	143

BW = Body weight; olanzapine = initial dose; PANSS = baseline assessment.

Method

Subjects

We recruited 5 male and 4 female patients, who met the DSM-IV criteria for schizophrenia in the acute psychotic phase of their illness, from the inpatients of the Department of Psychiatry of the National Cheng Kung University Hospital. Patients with any of the following conditions were excluded: (1) history of major medical or neurological diseases; (2) history of alcohol or substance dependence or abuse; (3) history of head injury; (4) receiving any antipsychotics other than olanzapine weeks before this study, and (5) receiving electroconvulsive therapy. Four patients took an initial olanzapine dose of 10 mg, while the remaining 5 patients took 20 mg. The patients were carefully evaluated for efficacy and side effects for up to 72 h prior to visiting the physician. To adjust their olanzapine medication to the optimal dose for long-term management, the patients were followed for up to 2 weeks. If psychosis had not subsided in 4 h at 20 mg, he or she was excluded from this study. During the treatment, the patients were also given benzodiazepines, anticholinergics and propranolol if necessary.

The Ethics Committee for Human Research at the National Cheng Kung University Medical Center had approved the study protocols. Informed consent was obtained from the patients and their key caregivers before the tests were performed.

Measures

The body mass index (BMI) was calculated by dividing the weight (in kilograms) by the squared height (in meters). Serum leptin measurements were taken at baseline, at 2 and 4 h, and on days 3, 7 and 14 after the initial dose of olanzapine. The samples were then centrifuged. The sera were analyzed immediately or stored at -70°C . Leptin concentrations were assessed by direct sandwich ELISA (Linco Research, St. Charles, Mo., USA). The lowest level of human leptin that can be detected by this assay is 0.5 ng/ml. The intra- and interassay coefficients of variation were 7 and 9%, respectively.

Statistics

Friedman tests were used to compare the differences in leptin level and BMI over 14 days. Posttreatment measurements were compared to the baseline (Friedman test) and corrected with $p < 0.01$ (2-tailed). All analyses were performed using the SPSS computer package (SPSS Inc., Chicago, Ill., USA).

Results

The average age of the subjects was 35 ± 10 years. The mean cumulative dosage of olanzapine after 14 days of treatment was 236 ± 56 mg. Three patients took propranolol with the first dose of olanzapine. All other epidemiologic data are shown in table 1. The patients gained 1–10 kg in weight during the 14-day olanzapine treatment. There was a nonsignificant increase in BMI on day 14 of the treatment (fig. 1). The BMI changes correlated inversely with the pretreatment leptin levels ($r = -0.93$, $p < 0.05$) after controlling for sex. Moreover, the leptin plasma levels increased significantly ($p = 0.003$) 4 h after the first dose of olanzapine. However, the plasma leptin levels on day 14 were not significantly different from those before treatment ($p = 0.06$; table 2).

Discussion

Previous studies have revealed weight gains and elevation in leptin levels weeks after the initiation of olanzapine treatment [14, 17–20]. Melkersson and Hulting [14] therefore proposed that olanzapine might alter

Table 2. BMI and leptin plasma levels over 14 days in schizophrenic inpatients receiving olanzapine treatment

Measure	Baseline	2 h	4 h	72 h	Day 7	Day 14	Statistics
<i>Plasma leptin levels, ng/ml</i>							
n	9	9	9	9	9	7	
Mean $\pm$ SD	14.6 $\pm$ 16.6	18.6 $\pm$ 19.9	21.7 $\pm$ 23.8	13.9 $\pm$ 11.7	15.7 $\pm$ 16.3	21.5 $\pm$ 17.5	$\chi^2 = 14.67$; $p = 0.01$
<i>Posthoc analysis</i>							
χ^2		2.00	9.00	0.00	0.50	3.57	
p	–	0.16	0.003*	1.00	0.48	0.06	
<i>BMI</i>							
n	8	8	8	8	8	6	
Mean $\pm$ SD	23.7 $\pm$ 3.7	23.7 $\pm$ 3.7	23.7 $\pm$ 3.7	23.8 $\pm$ 3.7	24.0 $\pm$ 3.9	24.8 $\pm$ 3.7	$\chi^2 = 7.94$; $p = 0.16$

Statistics: Friedman test, $p < 0.05$ (2-tailed). Posthoc analysis: posttreatment measurements were compared with baseline (Friedman test) corrected with $p < 0.01$ (2-tailed).

Fig. 1. Leptin plasma level over 14 days olanzapine treatment.

leptin regulation. In the current study, the results demonstrated a surge in circulating leptin levels before weight gain during olanzapine treatment. Moreover, the increase in BMI was preceded by a significant increase in leptin levels.

Although the mechanism remains unknown, we speculate that the rapid elevation in circulating leptin levels is regulated by the direct effects of olanzapine on the human sympathetic nervous system [21, 22], not secondary to the increasing body fat, since there may be interactions between leptin and the human sympathetic nervous sys-

tem [23, 24]. The timing of circulating leptin profile change following olanzapine administration is also consistent with the pharmacokinetic characteristics of olanzapine ($T_{\max}$ after orally administering one 10-mg dose of olanzapine is 3.75 h) [25]. Kraus et al. [20] reported that the weight gains induced by olanzapine persist even when leptin levels elevate. The elevation in leptin levels may not be a consequence of olanzapine-induced weight gains, since elevated circulating leptin levels should curb the desire for further food intake and therefore inhibit weight gain [8–10]. The persistent elevation in leptin levels may reflect a loss of the normal inhibitory control of leptin on body mass in patients with schizophrenia [26]. Interestingly, Wilson et al. [27] have shown that leptin plays an important role in maintaining homeostasis of the hypothalamic-pituitary-adrenal axis through diverse interactions. Moreover, drug-naïve schizophrenic patients are reported to have higher rates of impaired glucose tolerance and more intra-abdominal fat than non-schizophrenic individuals with dysregulation of the hypothalamic-pituitary-adrenal axis [28, 29].

The results of the present study need to be interpreted with caution due to the following limitations. First of all, this study only included a small number of patients. Secondly, weight gain or obesity is a complicated phenomenon, and many factors such as diurnal change and gender could confound the leptin levels. Previous reports have demonstrated that, in man, leptin levels peak at night and fall to a nadir the next morning [30]. Elimam et al. [31] also found marked diurnal changes in plasma leptin levels, with a nocturnal peak at 2 a.m., which was 60% higher than the lowest value at 10 a.m. As a result, the change in

leptin levels shown in our study may be partially attributable to this physiological diurnal variation in leptin levels, rather than completely caused by olanzapine treatment. Thirdly, the leptin level and BMI changes were not followed long enough for the results to be conclusive. Hence, a large-scale and longer-term study in which the confounding factors are controlled is needed in the future.

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