

Nizatidine treatment and its relationship with leptin levels in patients with olanzapine-induced weight gain

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It has been reported that nizatidine may reduce the weight gain in schizophrenic patients receiving olanzapine treatment. Previous studies have demonstrated a relation between olanzapine-induced weight gain and serum leptin levels. Therefore, in the present study, it was planned to investigate the efficacy of nizatidine on the treatment of olanzapine-induced weight gain, and if available, whether leptin levels were associated with reductions in weight gain. Of the patients with schizophrenia on olanzapine treatment, 59 who gave informed consent entered a 3 month open-label screening period. Of them, 35 patients (59%) showed weight gain in excess of 2.5 kg. These patients were randomly divided into two groups; olanzapine plus nizatidine (group I) and olanzapine plus placebo (group II) for an 8-week double-blind phase. The patients were evaluated at the baseline and at week 8 with respect to the positive and negative syndrome scale, body mass index, weight and serum leptin levels. In the open-label period, olanzapine led to a considerable marked increase in weight and in serum leptin levels. There was no statistically significant difference between the groups with respect to weight at the beginning of the 8-week double-blind treatment period. Throughout the 8 week double-blind period, in group I, the weight decreased by 4.5 ± 2.2 kg ($p < 0.05$). In contrast, weight increased in group II by a mean of 2.3 ± 0.9 kg ($p > 0.05$). The leptin levels decreased by 4.4 ± 2.3 ng/ml in group I ($p < 0.01$), and increased by 1.8 ± 0.6 ng/ml in group II ($p > 0.05$). These changes were accompanied by changes in the leptin levels in both groups I and II. It is concluded that leptin seems to be strongly associated with olanzapine-induced weight gain and that nizatidine treatment may reduce the weight gain and the correlated leptin levels in patients with schizophrenia on olanzapine treatment. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — leptin; nizatidine; olanzapine; weight gain

INTRODUCTION

Weight gain is a common side-effect of antipsychotic drugs (Brady, 1989; Osser *et al.*, 1999). The factors influencing body weight in patients receiving an antipsychotic drug are probably complex. A variety of factors, e.g. inactivity, social isolation, socioeconomic status and unemployment, may contribute to weight gain. On the other hand, changes in reproductive hormones affect weight gain in patients on chronic antipsychotic treatment (Baptista *et al.*, 2000).

A large body of studies has recently focused on leptin, an adipocyte hormone, levels in a variety of psy-

chiatric disorders (Kraus *et al.*, 2001; Atmaca *et al.*, 2002a,b,c,d,e). The plasma levels of leptin are considerably correlated with the body mass index (BMI) and the percent body fat. Leptin affects the intracellular lipid concentration by a decrease in the synthesis of fatty acid and triglycerides and an increase in lipid oxidation (Auwerx and Staels, 1998). Leptin administration reduced food intake and weight, suggesting its role in weight regulation (Halaas *et al.*, 1995). Furthermore, an interaction has been shown between leptinergic and serotonergic systems in the central nervous system (Liebowitz and Alexander, 1998).

A 5-HT_{2C} receptor blockade effect of antipsychotics has been discussed as a possible cause of the increase in food intake and related weight gain (McIntyre *et al.*, 2001). Olanzapine and clozapine have a strong affinity to serotonin and histamine receptors (5-HT_{2a}, 5-HT_{2c} and H₁). There is strong evidence that blockade of

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these receptors is associated with weight gain (Stahl, 1998). The weight gain induced by clozapine and olanzapine has been reported to be associated with an increase in leptin levels (Kraus *et al.*, 1999; Atmaca *et al.*, 2002d). Some studies have suggested that H₂ receptor antagonists might induce weight loss in overweight conditions (Stoa-Birketvedt *et al.*, 1996, 1998). On the other hand, Sacchetti *et al.* (2000) reported that nizatidine, an H₂ receptor antagonist, led to a considerable weight loss in two schizophrenic patients on olanzapine treatment. Therefore, in the present study, it was planned to investigate the efficacy of nizatidine on the treatment of olanzapine-induced weight gain, and, if available, whether leptin levels were associated with reductions in weight gain.

METHODS

Patients

Of the patients who had applied to Firat University School of Medicine Department of Psychiatry and were given olanzapine, with the diagnosis of schizophrenia according to DSM-IV, 59 took part in the study and gave written informed consent after complete description of the study. The study protocol was approved by the Local Ethics Committee of the Firat University School of Medicine. The clinical evaluation was performed by one trained psychiatrist for all patients. A semi-structured interview was carried out in order to establish the diagnosis of DSM-IV. Patients with comorbid axis 1 disorder were excluded. Exclusion criteria included the presence of a severe physical illness, the history of alcohol and substance abuse or dependence, a previous history of lipid lowering treatment and the presence of any endocrinological disorder. All participants were carefully assessed to exclude autoimmune, pulmonary, infectious diseases and neoplasms. No patient attended weight management classes, exercise classes or received dietary advice during the study. First of all, 59 patients (17 from in-patient and 42 from out-patient departments) entered 3 months of the open-label screening phase. All patients received monotherapy consisting of olanzapine, and the only concomitant medications permitted were biperiden hydrochloride (in two patients) and benzodiazepine (in five patients) derivatives. The daily dose of olanzapine ranged from 5 to 25 mg (the mean dose 15.3 mg/day). Before being treated with olanzapine, 29 patients were treated with conventional antipsychotics, seven patients were treated with risperidone, and four patients had no pharmacological treatment. In this period, seven were

excluded from the study due to a requirement for an additional drug (chlorpromazine use in seven patients), and discontinuation because of intolerance ($n = 5$). Of the rest, ten exhibited minor weight gain (1.5 kg and less) while two patients had weight loss. Therefore, 35 patients were enrolled in the 8-week, double-blind and placebo-controlled phase. In these patients, increases in weight ranged from 2.6 to 10.8 kg in the open-label screening phase.

At the beginning of the 8-week, double-blind and placebo-controlled phase, the subjects were randomly assigned to two groups; antipsychotic plus nizatidine (group I) ($n = 18$) or plus placebo (group II) ($n = 17$). The random assignment was in double-blind fashion. Nizatidine (150 mg b.i.d.) or placebo (one pill b.i.d.) was added to the ongoing olanzapine treatment.

All subjects were evaluated by a semi-structured questionnaire form which was arranged by the authors in accordance with clinical experience and available information sources. In addition, BMI was calculated by dividing the weight (kg) by the squared height (m) ($BMI = \text{kg}/\text{m}^2$). The patients were evaluated at the baseline and at week 8 with respect to the positive and negative syndrome scale (PANSS) (Andreasen, 1983, 1984), BMI, weight and serum leptin levels.

Determination of serum leptin levels

To determine serum levels of leptin, venous blood samples were obtained at 08.00 a.m. after overnight fasting. The leptin levels were measured using the DRG Diagnostics kit (DRG Instruments GmbH, Germany) in an enzyme-linked immunoassay (ELISA) method.

Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS/PC 9.05 version, 1998). A chi-square test was used to compare categorical variables. The group mean differences were examined by means of *t*-test or analysis of variance (ANOVA). The General Linear Model command of the SPSS was used when controlling for covariates. Correlation analysis was performed by Pearson correlations and Spearman rank correlations test, whenever appropriate. Differences were considered significant at $p < 0.05$ for all these tests.

RESULTS

All but one patient completed the 8-week double-blind treatment period. One patient from group I chose to seek an alternative form of treatment, so

the data from group I include 17 patients. The mean age was 27.1 ± 7.3 years in group I and 28.7 ± 8.8 in group II ($p > 0.05$). The mean duration of illness was 5.6 ± 3.2 and 6.1 ± 4.1 years in groups I and II, respectively ($p > 0.05$). With respect to the sex distribution, there were 7 females and 11 males in group I, and 7 females and 10 males in group II ($p > 0.05$). There was no difference regarding being chosen from in- or out-patient departments between groups (3 from in- and 14 from out-patient department in group I and 4 from in- and 13 from out-patient department in group II) ($p > 0.05$). At the evaluation at week 8, the mean doses were 14.7 ± 6.8 mg/day for group I and 13.8 ± 5.4 mg/day for group II ($p > 0.05$).

At the beginning of the open-label screening phase, the mean weight for all the patients in groups I and II was 62.6 ± 5.7 kg, whereas it was 67.1 ± 6.2 kg at the end of this period, with a mean of 66.7 ± 6.3 kg in group I and 67.4 ± 7.2 kg in group II ($p > 0.05$). In group I, weight decreased from a mean of 66.7 ± 6.3 kg to 62.2 ± 5.2 kg, a decrease of 4.5 ± 2.2 kg ($p < 0.05$). The weight increased in group II, with a mean of 2.3 ± 0.9 kg (from 67.4 ± 7.2 kg to 69.7 ± 7.6 kg) ($p > 0.05$).

No statistically significant difference regarding a decrease in the mean PANSS scores between groups was found ($p > 0.05$).

At the beginning of the open-label screening phase, the mean leptin level for all the patients in the groups I and II was 6.8 ± 3.5 ng/ml, whereas it was 10.9 ± 4.1 ng/ml at the end of this period, with a mean of 11.1 ± 4.2 ng/ml in group I and 10.7 ± 2.9 ng/ml in group II ($p > 0.05$). The leptin levels decreased in group I ($p < 0.01$), and increased by 1.8 ± 0.6 ng/ml in group II ($p > 0.05$). At the evaluation at week 8, a significant difference in the mean serum leptin levels between groups was found after BMI or age adjustment ($F = 7.2$, $p < 0.001$ adjusted for BMI; $F = 3.3$, $p < 0.05$ adjusted for age). In addition, when comparing the mean leptin levels between sexes within each group, a statistically significant difference was found in group I ($p < 0.05$), but not in group II ($p > 0.05$).

The mean changes in BMI for groups I and II were -2.4 ± 1.3 and 0.5 ± 0.3 kg/m², respectively ($p < 0.05$). At the evaluation at week 8, a significant difference in the mean BMIs among groups was found after sex or age adjustment ($F = 3.9$, $p < 0.05$ adjusted for sex; $F = 4.3$, $p < 0.05$ adjusted for age).

The weight, PANSS score, tryglyceride and leptin levels, and BMI at baseline and week 8 in the treatment groups are presented in Table 1.

The change in leptin levels was correlated with the change in BMI in both groups ($r = 0.61$, $p < 0.05$ for

Table 1. The weight, PANSS score, leptin levels and BMI at baseline and week 8 of double-blind period in the treatment groups

	Group I	Group II (n = 17)	p (n = 17)
Body weight (kg)			
Baseline	66.7 ± 6.3	67.4 ± 7.2	NS
Week 8	62.2 ± 5.2	69.7 ± 7.6	<0.05
p	<0.05	>0.05	
PANSS score			
Baseline	83.6 ± 7.3	81.1 ± 6.9	NS
Week 8	71.9 ± 4.1	73.8 ± 3.3	NS
p	<0.05	<0.05	
Leptin (mg/dl)			
Baseline	11.1 ± 4.2	10.7 ± 2.9	NS
Week 8	6.7 ± 3.1	12.5 ± 3.8	<0.001
p	<0.001	>0.05	
BMI			
Baseline	26.8 ± 1.7	26.4 ± 1.6	NS
Week 8	24.4 ± 2.1	26.9 ± 2.2	<0.05
p	<0.05	>0.05	

group I, and $r = 0.56$, $p < 0.05$ for group II), and with the change in weight in group I ($r = 0.65$, $p < 0.05$), but not in group II ($r = 0.10$, $p > 0.05$). On the other hand, between the changes in weight and BMI, there was a positive correlation in group I ($r = 0.56$, $p < 0.05$). No significant correlation was observed between changes in total PANSS scores and leptin levels in both groups ($r = 0.18$, $p > 0.05$ for group I, and $r = 0.12$, $p < 0.05$ for group II) or the change in weight ($r = 0.20$, $p > 0.05$ for group I, and $r = 0.08$, $p > 0.05$ for group II).

There were a total of 11 reports of newly observed adverse events. Of them, six were from four patients in group I and five were from three patients of group II ($p > 0.05$). The most frequently reported side effects in patients receiving nizatidine were dizziness ($n = 3$) and headache ($n = 2$).

DISCUSSION

To the best of our knowledge, the present study is the first to assess the longitudinal effects of nizatidine treatment on both body weight and serum leptin levels. The major findings of our study are as follows: (1) Olanzapine leads to a considerable marked increase in weight, and leptin level, and (2) nizatidine treatment may reduce the weight gain and correlated leptin levels in patients with schizophrenia on olanzapine treatment. Moreover, nizatidine is well-tolerated, and no drop-outs occurred owing to adverse events.

In a meta-analysis, it has been reported that of all the antipsychotics olanzapine is the one causing most weight gain (Allison *et al.*, 1999). In this meta-analysis,

the mean weight gain on olanzapine treatment at 10 weeks was 4.2 kg, which is comparable to our result of an increase of 4.5 kg within the open-label screening period. There are a variety of theories to explain antipsychotic-induced weight gain. One theory is a histamine-1 (H_1) receptor blockade by antipsychotics since H_1 receptors are considered to be involved in the regulation of food intake (Richelson, 1996). Olanzapine is among the most potent of the antipsychotics blocking H_1 receptors (Richelson, 1996). However, peripheral factors such as changes in reproductive hormones (Baptista *et al.*, 2000) have been also proposed. On the other hand, it has been reported that antagonism on serotonin, dopamine and norepinephrine receptors may be associated with weight gain, although the underlying mechanisms have remained obscure (Stahl, 1998).

In this study, an important finding was a considerable increase in leptin levels associated with olanzapine use. Olanzapine-induced increase in leptin levels has been previously reported (Melkersson *et al.*, 2000; Atmaca *et al.*, 2002d). Leptin has been considered to interact with some neurotransmitters including histamine and serotonin (Dryden *et al.*, 1999; Morimoto *et al.*, 1999). Serotonin is a well-known important satiety factor. Despite the fact that it is not well understood which serotonin receptors are critical an increase in serotonin at different serotonin receptors has been demonstrated to decrease food intake and in contrast a serotonin blockade causes an increased energy intake (Meguid *et al.*, 2000; De Vry and Schreiber, 2000). The $5-HT_{2C}$ has been reported to be a candidate receptor for psychotropic-induced weight gain and antagonists of this receptor produce weight gain (Tecott *et al.*, 1995). An interaction between leptinergic and serotonergic systems in the central nervous system has been shown (Liebowitz and Alexander, 1998). It has been noted that leptin administration stimulated serotonin turnover (Calapai *et al.*, 1999), suggesting further evidence for this association. Olanzapine and clozapine have a strong affinity for serotonin and histamine receptors ($5-HT_{2a}$, $5-HT_{2c}$ and H_1). There is strong evidence that blockade of these receptors is associated with weight gain (Stahl, 1998). As mentioned above, leptin has been considered to interact with both histamine and serotonin (Dryden *et al.*, 1999; Morimoto *et al.*, 1999).

Another major finding of this study is that subchronic nizatidine treatment reduced olanzapine-induced weight gain and was correlated with leptin levels. It has been reported that H_2 receptor antagonists might induce weight loss in overweight conditions (Stoa-Birketvedt *et al.*, 1996, 1998). On the other

hand, Sacchetti *et al.* (2000) reported that nizatidine led to a considerable weight loss in two schizophrenic patients on olanzapine treatment. The present study has confirmed these studies. In animal and human studies, weight gain considerably increased circulating leptin concentrations while weight loss resulted in reduced leptin levels (Considine and Caro, 1997; Mantzoros *et al.*, 1997). As supported by the present study. An important cause of the olanzapine-induced increases in leptin levels may be overeating (Kraus *et al.*, 1999). However, an alternative route might be the reduction in feedback sensitivity of the central nervous system to the leptin signal. It has been hypothesized that the central histaminergic system is a target for leptin in its control of feeding and that it activates the histaminergic system in the hypothalamus, which may contribute to the expression of the leptin-induced anorectic effect (Morimoto *et al.*, 2000). Meanwhile, rodent studies suggest that the effects of H_2 receptor antagonism on weight loss may be mediated by increases in cholecystokinin (CCK) (Stoa-Birketvedt *et al.*, 1996, 1998). CCK, a hormone having anorexigenic effects, is one of the best studied peptides of the satiety system, which strongly affects meal size by influencing satiety by nutrient (Gibbs *et al.*, 1973). The short-term effects of CCK on food intake can be potentiated by leptin (Wang *et al.*, 2000). Additionally, leptin and CCK can also interact directly at the level of the paraventricular nucleus. As a result, it may be speculated that the decreases in weight and circulating leptin levels could be part of a cascade reaction initiated by the drug studied, and the observed alteration of the leptin levels would then be the consequence of effects on a complex mechanism that is incompletely understood.

There are some methodological limitations to this study that must be acknowledged. First, the relatively small sample size might not be representative of the patients treated with olanzapine. Furthermore, it was not possible to test if poor economic status and other psychosocial factors might be related to serum leptin levels. However, it should be mentioned that the out-patients come from similar socioeconomic regions to the subjects who were in-patients receiving a routine hospital diet and there was no difference in the ratio of in/out-patient between the groups. In conclusion, our results suggest that leptin seems to be strongly associated with olanzapine-induced weight gain and that nizatidine treatment may reduce the weight gain and correlated leptin levels in patients with schizophrenia on olanzapine treatment. Our results need to be confirmed by studies with a large number of patients.

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