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Nizatidine for the treatment of patients with quetiapine-induced weight gain

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It has been reported that nizatidine may reduce weight gain in schizophrenic patients on olanzapine treatment. Leptin has been reported to be associated with antipsychotic-induced weight gain. Thus, the purpose of the study was to evaluate whether nizatidine might be useful for the treatment of quetiapine-induced weight gain. Among the patients on the quetiapine monotherapy, 47 participated in the study for the two and half months of the open-label screening period. However, 28 patients who gained considerable weight in this period entered the 8-week, double-blind and placebo-controlled phase. These patients were randomly divided into two groups; quetiapine plus nizatidine (group I) and quetiapine plus placebo (group II) for the 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. The mean weight and leptin levels exhibited modest increases in both groups for the open-label screening period. In the double-blind period, in group I, a minimal, but not statistically significant, decrease in weight was observed, with a mean of 1.0 ± 0.6 kg. The weight increased in group II. The leptin levels decreased by a mean of 0.6 ± 0.6 ng/ml in group I, and increased by 1.0 ± 0.9 ng/ml in group II. At evaluation at week 8, a trend toward statistical significance in the mean serum leptin levels between groups was detected. The results suggest that nizatidine treatment may stop but not reduce the weight gain and is correlated with leptin levels in patients with schizophrenia on quetiapine treatment. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — leptin; nizatidine; quetiapine; weight gain

INTRODUCTION

Weight gain is a common adverse effect of a variety of psychotropic drugs such as lithium, tricyclic antidepressants and antipsychotics (Berken *et al.*, 1984; Kraus *et al.*, 1999; Atmaca *et al.*, 2002c). Although both classical and atypical antipsychotics are known to induce weight gain (Brady, 1989; Osser *et al.*, 1999), atypical antipsychotics, especially olanzapine and clozapine appear to have greater potential to induce weight gain (Allison *et al.*, 1999). The factors influencing body weight in patients using an antipsychotic are probably complex, despite the fact that the effects of several neurotransmitter systems including serotonergic, dopaminergic and histaminergic systems may contribute to weight gain (McIntyre *et al.*, 2001). Leptin has recently attracted considerable interest in a variety of psychiatric disorders and psychotropic drug use (Kraus *et al.*, 2001; Atmaca *et al.*, 2002a,b,c,f). Leptin administration reduced food intake and weight, suggesting its role on 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). The 5-HT_{2C} receptor blockade effect of antipsychotics has been discussed as a possible cause of 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 H_1) which are associated with weight gain (Stahl, 1998). The weight gain induced by clozapine and olanzapine has been reported to be associated with an increase in the leptin levels (Kraus *et al.*, 1999). In our previous study, it was found that quetiapine has a modest effect on weight and is correlated with leptin levels (Atmaca *et al.*, 2002e). To the best of our knowledge, this is the

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first study to investigate the relationship between the nizatidine treatment, and both body weight and serum leptin levels in patients on quetiapine treatment. It has been suggested that H_2 receptor blockers induce weight loss (Stoa-Birkedvedt *et al.*, 1998). Sacchetti *et al.* (2000) noted that nizatidine led to considerable weight loss in two schizophrenic patients on olanzapine treatment. In our study (Atmaca *et al.*, 2002d), the results suggest that nizatidine treatment may reduce weight gain and be correlated with leptin levels in patients with schizophrenia on olanzapine treatment. Given the pharmacologic similarity of quetiapine and olanzapine, it was hypothesized that nizatidine might also decrease the quetiapine-induced weight gain and be correlated with leptin levels.

METHODS

Of the patients who applied to the Firat University School of Medicine Department of Psychiatry, were diagnosed with schizophrenia according to DSM-IV and received quetiapine monotherapy, 47 took part in the study and gave written informed consent after a complete description of the study. A semi-structured interview was carried out in order to establish DSM-IV diagnosis. The study protocol was approved by the Firat University School of Medicine Ethics Committee. Exclusion criteria included the presence of a severe physical illness, a 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. At first, 47 patients entered an open-label screening phase of at least two and half months (ranging from 2.5 months to 4 months). The only concomitant medications permitted were benzodiazepine derivates (lorazepam in four patients and diazepam in two patients) and biperiden hydrochloride (in one patient). Biperiden hydrochloride was allowed for acute dystonia and severe parkinsonian symptoms. The daily dose of quetiapine ranged from 300 to 750 mg (the mean dose 504.4 ± 68.1 mg/day). In this period, four were excluded from the study due to a requirement for additional drug, and discontinuation because of intolerance ($n = 2$). Of the remaining patients, ten exhibited negligible weight gain (0.9 kg and less) while three patients experienced weight loss. Thus, 28 patients entered the 8-week, double-blind and placebo-controlled phase. In these patients, the weight increase ranged from 2.3 to 7.2 kg.

The subjects were randomly divided into two groups; quetiapine plus nizatidine (group I) ($n = 14$) and quetiapine plus placebo (group II) ($n = 14$). The random assignment was in double-blind fashion. Nizatidine (150 mg b.i.d.) or placebo (one pill b.i.d.) was added to quetiapine.

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 (in kg) by the squared height (in m) ($BMI = kg/m^2$). 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.

The laboratory investigation included measurement of serum leptin levels. Venous blood samples were collected at 08.00 a.m. after overnight fasting. The leptin levels were measured in serum by enzyme-linked immunoassay (ELISA) method using the DRG Diagnostics Kit (DRG Instruments GmbH, Germany).

Group mean differences were examined by means of *t*-test or analysis of variance (ANOVA). A chi-square test was used to compare categorical variables. The general linear model command of the SPSS was used when controlling for covariates. Pearson correlations or Spearman Rank correlations test were used whenever appropriate for the correlation analyses. Differences were considered significant at $p < 0.05$ for all these tests.

RESULTS

All patients except three completed the 8-week double-blind treatment period. There was one premature discontinuation in group I at week 2 because of agitation, and two in group II, one at week 3, who wished to be discharged by his relatives and one at week 3 who was treatment incompliant. The mean age was 31.2 ± 7.9 years in group I and 29.1 ± 8.1 in group II ($p > 0.05$). There were seven males and six females in group I, and six males and six females in group II ($p > 0.05$). No significant difference regarding the mean duration of illness was found between groups (3.8 ± 2.2 and 4.4 ± 2.9 years in groups I and II, respectively) ($p > 0.05$). At evaluation at week 8, the mean doses were 479.2 ± 60.9 mg/day for group I and 492.7 ± 72.2 mg/day for group II ($p > 0.05$).

At the beginning of the open-label screening phase, the mean weight of the patients in groups I and II was 66.8 ± 4.1 kg, whereas it was 70.6 ± 5.5 kg at the end of this period ($p < 0.05$). There was no statistically significant difference between the groups regarding the weight at the beginning of the 8-week double-blind treatment period, being 70.2 ± 4.8 kg in group I

Table 1. Weight, PANSS score, leptin levels and BMI at baseline and week 8 in the treatment groups

	Group I ($n=17$)	Group II ($n=17$)	p
Body weight (kg)			
Baseline	70.2 ± 4.8	71.1 ± 5.6	NS
Treatment	69.2 ± 5.2	72.3 ± 5.9	NS
p	>0.05	>0.05	
PANSS score			
Baseline	80.2 ± 6.5	83.5 ± 7.1	NS
Treatment	72.1 ± 4.1	74.4 ± 4.9	NS
p	<0.05	<0.05	
Leptin (mg/dl)			
Baseline	8.5 ± 2.8	8.8 ± 3.1	NS
Treatment	7.9 ± 2.5	9.8 ± 3.3	NS
p	>0.05	>0.05	
BMI			
Baseline	27.1 ± 1.3	26.8 ± 1.7	NS
Treatment	26.6 ± 1.1	27.4 ± 1.9	NS
p	>0.05	>0.05	

and 71.1 ± 5.6 kg in group II ($p > 0.05$). In group I, a minimal, but not statistically significant, decrease in the weight was observed, with a mean of 1.0 ± 0.6 kg ($p > 0.05$). The weight increased in group II, with a mean of 1.2 ± 1.2 kg (from 71.1 ± 5.6 kg to 72.3 ± 5.9 kg) ($p > 0.05$).

At the beginning of the open-label screening phase, the mean leptin level for the patients in groups I and II was 5.3 ± 2.3 ng/ml, whereas it was 8.7 ± 3.2 ng/ml at the end of this period ($p < 0.05$), with a mean of 8.5 ± 2.8 ng/ml in group I and 8.8 ± 3.1 ng/ml in group II ($p > 0.05$). In the double-blind phase, the leptin levels decreased by 0.6 ± 0.6 ng/ml, from a mean of 8.5 ± 2.8 ng/ml to 7.9 ± 2.5 ng/ml in group I ($p > 0.05$), and increased by 1.0 ± 0.9 ng/ml, from a mean of 8.8 ± 3.1 ng/ml to 9.8 ± 3.3 ng/ml in group II ($p > 0.05$). At the evaluation at week 8, in analyses controlling for BMI or age, a trend toward statistical significance in the mean serum leptin levels between groups was detected ($F = 2.9$, $p = 0.07$ adjusted for BMI; $F = 2.6$, $p = 0.06$ adjusted for age). In addition, when comparing the mean leptin levels between sexes within each group, no statistically significant difference was found in either group ($p > 0.05$).

The mean changes in BMI for groups I and II during the double-blind period were -0.5 ± 0.4 and 0.6 ± 0.4 kg/m^2, respectively ($p < 0.05$). At the evaluation at week 8, no significant difference in mean BMIs between the groups was found after adjustment for sex or age ($F = 0.09$, $p > 0.05$ adjusted for sex; $F = 1.8$, $p > 0.05$ adjusted for age).

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

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

The change in leptin levels was correlated with a change in BMI in both groups ($r = 0.58$, $p < 0.05$ for group I, and $r = 0.53$, $p < 0.05$ for group II). On the other hand there was a positive correlation in group I between the changes in weight and BMI ($r = 0.56$, $p < 0.05$). No significant correlation was observed between changes in total PANSS scores and leptin levels in either group ($r = 0.06$, $p > 0.05$ for group I, and $r = 0.18$, $p < 0.05$ for group II) or the change in weight ($r = 0.13$, $p > 0.05$ for group I, and $r = 0.10$, $p > 0.05$ for group II).

DISCUSSION

In keeping with a previous report regarding the effects of quetiapine on weight (Atmaca *et al.*, 2002e), the present study provides further evidence that schizophrenic patients on quetiapine treatment exhibit modest increases in weight and leptin levels compared with those treated with olanzapine and clozapine. As atypical antipsychotics, clozapine and olanzapine lead to considerable weight gain and induce leptin, which is known to be involved in weight regulation (Kraus *et al.*, 1999), it might be expected that another atypical antipsychotic, quetiapine would have similar effects on weight, having a similar receptor binding capacity to clozapine and olanzapine. There are various theories to explain differential effects of antipsychotics on leptin levels. This may be associated with the antipsychotics' differential effects on various neurotransmitter systems which are involved in the regulation of weight (5-HT_{2a}, 5-HT_{2c} and H_1). Leptin has been considered to interact with some neurotransmitters including histamine and serotonin (Dryden *et al.*, 1999; Morimoto *et al.*, 1999). Olanzapine and clozapine have stronger affinity to serotonin and histamine receptors (5-HT_{2a}, 5-HT_{2c} and H_1) compared with conventional antipsychotics and quetiapine. There is strong evidence that blockade of these receptors is associated with weight gain (Stahl, 1998).

Another major finding of this study is that subchronic nizatidine treatment stopped the weight gain rather than reducing quetiapine-induced weight gain. Unexpectedly, we found that schizophrenic patients with weight gain failed to demonstrate considerable decreases in weight and leptin levels due to nizatidine treatment, although nizatidine can stop a gain in weight for a duration of 8 weeks. In our unpublished study, we found that nizatidine treatment might reduce weight gain and the correlated leptin levels in patients

with schizophrenia on olanzapine treatment. Given the pharmacologic similarity of quetiapine and olanzapine, we hypothesized that nizatidine might also decrease the quetiapine-induced weight gain. However, the effects of the nizatidine are not completely in line with our hypothesis. It has been reported that H_2 receptor antagonists might induce weight loss in overweight conditions (Stoa-Birkedvedt *et al.*, 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 partially confirmed these studies. In animal and human studies, weight gain considerably increases circulating leptin concentrations while weight loss results in reduced leptin levels (Considine and Caro, 1997; Mantzoros *et al.*, 1997), as supported by the present study. 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 a leptin-induced anoreic effect (Morimoto *et al.*, 1999). In our study (Atmaca *et al.*, 2002d), nizatidine considerably decreased olanzapine-induced weight gain and the correlated leptin levels. We do not know the exact reason for this difference. The differential effects of nizatidine on quetiapine and olanzapine-induced weight gain may be attributed to probable differential cascade reactions which might be initiated by the drug studied.

The limitations of the present study included the small sample size which might not be representative of the patients treated with quetiapine. Furthermore we could not control the effects of dietary changes. In conclusion, the results suggest that nizatidine treatment may stop and but not considerably reduce the weight gain and correlated leptin levels in patients with schizophrenia on quetiapine treatment. Our results appear to justify studies with a larger number of patients to confirm that nizatidine treatment may be useful in patients with quetiapine-induced weight gain.

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