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Weight Gain Associated With the −759 C/T Polymorphism of the 5HT2C Receptor and Olanzapine

Vicki L. Ellingrod,[1]* Paul J. Perry,[1,2] John C. Ringold,[3] Brian C. Lund,[1] Kristy Bever-Stille,[1] Frank Fleming,[2] Timothy L. Holman,[1,2] and Del Miller[2]

[1]*University of Iowa, College of Pharmacy, Iowa*
[2]*University of Iowa, College of Medicine, Department of Psychiatry, Iowa*
[3]*University of Iowa, College of Medicine, Department of Surgery, Iowa*

Background: Weight gain from atypical antipsychotic use has become a significant problem. Recent reports have liked the −759 polymorphism of the 5HT2C receptor and obesity as well as weight gain from chlorpromazine, risperidone, and clozapine. Aim: To determine associations between weight gain during olanzapine treatment and the −759 C/T polymorphism of the *5HT2C* receptor gene. Methods: This study included 42 acutely ill patients with schizophrenia (DSM-IV). Weekly assessments included Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Negative Symptoms (SANS), and weight measurements. Olanzapine was titrated to a fixed dose (7.5–20 mg/day) for 2–6 weeks. A 24 hr plasma level was obtained at the endpoint visit. Genomic DNA was isolated from a whole blood sample and analyzed for the −759C/T polymorphism of the 5HT2C receptor. Results: A chi-square analysis was conducted comparing the distribution of T and C alleles in subjects grouped as gaining more or less than 5, 7, and 10% of their baseline weight during treatment with olanzapine. A threshold of 10% was found to be significant. The distribution of T alleles was higher in subjects not gaining 10% of more of their body weight compared who did gain significant weight (11/27 (40.7%) vs. 0/15 (100%), $\chi^2 = 11.805$, $P = 0.0035$). Conclusions: Subjects with a T allele of the 5HT2C receptor −759C/T polymorphism may have a lower incidence of weight gain from olanzapine over a 6 week period compared to those with the C allele. These results need to be replicated. © 2005 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; serotonin; weight gain; olanzapine; polymorphisms; antipsychotics

INTRODUCTION

Atypical antipsychotic (AAP) induced weight gain is a significant adverse effect facing clinicians and patients with schizophrenia. Estimates suggest that more than half of those treated with AAPs will gain at least 10% of their initial body weight over the course of therapy, although some have been reported to gain more than 40% [Umbricht and Kane, 1996]. In general a weight gain of 5% or more over ideal body weight within 1–2 months places individuals at risk for significant health complications such as hypertension, type II diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and respiratory problems [Allison et al., 1999a].

The *5HT2C* receptor gene is located on the X chromosome at q24 [Lappalainen et al., 1995] and has a polymorphism consisting of a C to T transversion at position −759 in the 5′ flanking region. The site of this polymorphism contains regulatory and putative transcription factor binding regions [Shih et al., 1996] which may result in alterations in the expression of the gene. Other investigators have found that mice lacking the 5HT2C receptor are obese and the activation of 5HT2C results in decreased eating behaviors [Tecott et al., 1995; Stahl, 1998]. Recently, this polymorphism has been hypothesized as having a relationship with the development of type II diabetes and obesity in a normal control population [Yuan et al., 2000], where an excess of the T allele was found in non-obese subjects. Additionally, an excess of the T allele has been found in patients with schizophrenia receiving chlorpromazine, risperidone, and clozapine who did not development significant weight gain (>7%) over their baseline weight [Reynolds et al., 2002, 2003]. Although others have not found this association [Basile et al., 2002; Tsai et al., 2002]. The aim of this study was to examine the relationship between the −759C/T polymorphism of the 5HT2C receptor and weight gain during treatment with olanzapine.

SUBJECTS AND METHODS

Subjects and Clinical Measures

All subjects were recruited through Iowa's Mental Health Clinical Research Center (MHCRC) in-patient unit and consisted of 42 subjects who met DSM-IV criteria for schizophrenia. Ratings scales included the Brief Psychiatric Rating Scale (BPRS) [Overall and Gorham, 1962] and the Scale for Assessment of Negative Symptoms (SANS) [Andreasen, 1983]. These were completed at baseline and then weekly to assess psychopathology and medication side effects. Additionally, each subject's weight and vital signs were obtained at each study visit. Prior to study entry, subjects underwent a physical exam to assure they were physically healthy.

All subjects gave written informed consent to the protocol approved by the University of Iowa Human Subjects Institutional Review Board. The consent process was ongoing and the subjects were regularly reminded throughout study that their participation was voluntary.

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*Correspondence to: Vicki L. Ellingrod, Pharm.D., BCPP, S413 Pharmacy Building, Iowa City, Iowa 52242.
E-mail: vicki-ellingrod@uiowa.edu

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Olanzapine Dosing

Subjects were started on olanzapine at the first visit and then titrated to a fixed dose ranging from 7.5 to 20 mg/day. An olanzapine level was obtained after 1 week and at endpoint. Dosage adjustments were performed to assure olanzapine plasma concentrations were greater than 9.3 ng/ml [Perry et al., 1997]. Olanzapine was continued for a total of 6 weeks, of which 4 weeks was at a fixed dose.

Genotyping

DNA was analyzed for the −759 C/T polymorphism of the 5HT2C receptor using methods by Yuan et al. [2000]. Using PCR, a fragment from −855 to −634 of the receptor's sequence was amplified. This fragment was then digested with *Aci I* in order to determine each subject's genotype. In subjects where there was a question about genotype, the PCR product was directly sequenced. The results of the restriction digest were run on a 10% polyacrylamide gel stained with ethidium bromide. All genotyping procedures were conducted after each subject completed the study to blind the raters to genotype status.

Statistical Analysis

A chi-square analysis (Fisher's exact test) was conducted comparing the distribution of T and C alleles in subjects grouped as gaining more or less than 5, 7, and 10% of their baseline weight during treatment with olanzapine. A P-value less than 0.05 was considered statistically significant. Differences between group means and socio-demographics were determined by the use of the Student's unpaired t-tests as well as change scores for the BPRS and SANS. Change scores were based on the last observation carried forward method.

RESULTS

A total of 42 Caucasian subjects were included in this analysis, of which eight were female. There were no differences in socio-demographics or psychopathology between the groups of subjects with the various genotypes at baseline with the exception of the less women being in the C allele group (3 vs. 5) ($P = 0.01$). The mean endpoint dose of olanzapine was 12.8 ± 3.12 mg/day and the mean endpoint serum concentration was 23.9 ± 16.38 ng/ml taken 24 hr post dose. There was no difference in the mean dosage of olanzapine between the C and T allele groups (12.75 ± 2.88 mg/day vs. 13.18 ± 3.88 mg/day, $P = 0.70$). There was a difference in the number of subjects between the two allele groups who needed an increase in dosage after week one, but this was not significant (30 subjects with the C allele vs. 12 subjects with the T allele) ($P = 0.49$).

The allele frequencies of the C and T alleles for the whole group were 78 and 22%, respectively. The frequency of the T allele was 17.6% in the male subjects and 31% in the female subjects. The distribution of T alleles was higher in subjects not gaining 10% of more of their body weight compared who did gain significant weight (11/27 (40.7%) vs. 0/15 (100%), $\chi^2 = 11.805$, $P = 0.0035$) (Table I). This analysis was not significant for the 5 and 7% weight thresholds. All of the subjects, who gained >10% of their initial body weight over 6 weeks, had at least one C allele. Subjects with a C allele gained a mean of 12.2 ± 9.7% over their initial body weight compared to subjects with a T allele who gained a mean of 4.7 ± 4.2%. There were no statistical differences in the percentage change in SANS and BPRS scores or olanzapine dosage or blood level between the groups of subjects when categorized according to weight or genotype (Tables II and III).

TABLE I. Distribution of C and T Alleles Based on Weight Gained

Weight gain (%)	C allele	T allele
>10	15	0
<10	16	11

Chi-square analysis for weight gain >10% distributed by 5HT2CR −759 genotype (two tailed $P = 0.0035$).

DISCUSSION

From these data, we can conjecture a potential protective effect of the T allele on lack of significant weight gain (≥10% over baseline) following 6 weeks of olanzapine treatment, although this could be an incidental finding. Previous authors have shown that in subjects without schizophrenia, the frequency of the variant T allele was higher in non-obese [Yuan et al., 2000]. This relationship may be due to higher transcription levels of this gene which plays a part in appetite regulation resulting in more resistance to obesity. Additionally, Reynolds et al. [2002] showed that in patients being treated with chlorpromazine and risperidone for 6 weeks, 51% of those with a C allele had gained more than 7% of their initial body weight, while only 15% of those with T allele met this criterion. Additionally, these same authors [Reynolds et al., 2003], found that for subjects receiving clozapine for 6 months, a very similar relationship was true in that the body mass index of subjects with a T allele was significantly less than that for subjects with a C allele (0.32 kg/m^2 vs. 1.12 kg/m^2, $P < 0.02$).

This is the first study to examine the relationship between the −759C/T polymorphism of the 5HT2C receptor and olanzapine. Although, genetics may play a role in the development of significant weight gain from atypical antipsychotics, additional factors need to be taken into consideration such as diet, exercise, and schizophrenia symptomatology. Unfortunately, diet and exercise were not monitored due to the naturalistic nature of this study.

Anecdotally it has been suggested that patients who gain the most amount of weight from atypical antipsychotics do the best clinically [Basson et al., 2001] although in comparing subjects based on the 10% weight gain threshold, no significant differences in psychopathology were found (Table III). Additionally, there were no differences in the dosage (mg/day) or blood level of olanzapine between these two groups (Table III).

Thus, this preliminary study supports a potential relationship between the −759C/T polymorphism of the 5HT2C receptor and significant weight gain with olanzapine treatment. The allele distribution reveals 48% sensitivity (15/31) and 100% specificity (11/11) statistics (see Table I). This finding indicates that patients with the variant T allele may have a lower incidence of gaining substantial amounts of weight compared to patients with the C allele.

TABLE II. Differences in Changes in Psychopathology Based on Genotype Group

	C allele	T allele	P-value
Mean change (±SD) in SANS score	23.7% (38.8%)	27.2% (27.6%)	0.78
Mean change (±SD) in BPRS score	21.8% (24.6%)	24.2% (19.5%)	0.77
Mean weight (±SD) at baseline (kg)	79.9 (22.4)	85.2 (16)	0.48

TABLE III. Differences in Changes in Psychopathology, and Olanzapine Dose and Plasma Level Based on Weight Gain Threshold of 10%

	≥10% Weight gain	<10% Weight gain	*P*-value
Mean change (±SD) in SANS score	28% (30.4%)	23% (38.6%)	0.69
Mean change (±SD) in BPRS score	29.5% (24%)	18.5% (22%)	0.15
Mean olanzapine dose (±SD) at endpoint (mg/day)	13.6 (3.05)	12.4 (3.14)	0.26
Mean olanzapine plasma level (±SD) at endpoint (ng/ml)	27 (19.37)	22.19 (14.6)	0.36

Along with the prior study that has been done with risperidone, chlorpromazine, and clozapine, and their relationship with the −759C/T polymorphism, the results of this study may have important implications as we continue our search to determine the genetic factors involved in the development of antipsychotic weight gain. The clinical significance of the presence of the variant T allele may be important, but needs to be replicated in prospective trials, of a longer duration, with greater control of dietary and physiologic factors such as exercise. Due to these shortcomings additional research into the area of genetics, diabetes, and weight gain from atypical antipsychotics needs to be pursued.

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