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DOES FAMOTIDINE CAN PREVENT THE OLANZAPINE-INDUCED WEIGHT GAIN IN SCHIZOPHRENIA PATIENTS?

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ABSTRACT

Introduction: One of the most important concerns of schizophrenic patients that use the drug olanzapine, is side effect of weight gain and in some cases, the patient is obliged to refrain from the use of this drug. One of the drugs raised as a potential treatment for this condition is famotidine. Therefore, this study aimed at evaluating the effectiveness of famotidine in the process of weight changes of schizophrenic patients in a randomized clinical trial. **Materials and Methods:** This randomized clinical double-blind and placebo-controlled trial was conducted on 44 patients in the two groups include the famotidine and olanzapine group (n = 22) and the placebo and olanzapine group (n = 22). Patients ' weight and BMI were measured at baseline and 2, 4, 6 and 8 weeks after it. Then, data were analyzed using the SPSS version 14. **Results**: In both groups the weight and BMI in patients taking olanzapine increased during the study and the eighth week of the start of treatment. Although the trend of this increase in the additive famotidine group was significantly slower than the placebo. None of the patients showed a side effect of famotidine. **Conclusion**: Adding famotidine medication to the treatment process of olanzapine in patients with schizophrenia significantly reduces the effect of weight gain during use in patients.

KEYWORDS: Famotidine; Olanzapine; weight gain.

INTRODUCTION

Schizophrenia is the most serious psychiatric disorders in health systems around the world that has a prevalence of about 0.3- 0. 7% during the lifetime of a person.[1] This disease manifests itself usually in different ways from hallucinations and delusions to the

disorganized speech and thinking, and is associated with considerable social dysfunction.[2] Hence treatment and the appropriate management of this disease, is of a very high importance whether in terms of efficacy or in terms of safety.[3] For this purpose, the use of the olanzapine, as one of the most important components in the treatment of schizophrenia, is of particular appeal among psychiatrists.[4] Despite the high efficacy of olanzapine, this drug, like other second-generation antipsychotics (SGAs) cause side effects such as weight gain and impaired metabolic parameters. Several studies have shown that olanzapine causes weight gain of 0.9 kg per month, or an increase of 6-10 kg or more in one year after treatment.[5]

The exact mechanism of effects of olanzapine on body weight gain is still unknown. Despite this research, the effect of the drug on the appetite-stimulating receptors (caused by serotonin and histamine receptor stimulation) as well as increased insulin resistance, have been raised as possible factors involved in weight gain among the consumers.[6]

At present, H2 histamine receptors are considered as one of the major systems involved in the regulation of feeding behavior and weight.[7] This mechanism-based look leads to the creation of this view among some researchers, which inhibition of this system by the H2 antagonists such as cimetidine, nizatidine and famotidine can cause weight loss in patients treated with the olanzapine.[8] Of the medications H2 blockers, famotidine has fewer side effects and drug interactions with beta-adrenergic receptors, cholinergic and H1-receptor.[9,10] On the other hand, it is reported that this drug can have a positive impact on some aggressive risk and general psychopathology scale in patients with schizophrenia.[11]

Unfortunately, despite the perfect safety of this drug, as well as the potential impact of this agent in the treatment of weight gain caused by olanzapine, in accordance with the best of our knowledge, only one clinical trial has been done in this area.[12] While in the trial[12], famotidine was without the effects of lowering the weight, due to the small sample size (n = 14) and short duration of the study (six weeks), researchers decided to design the trial to evaluate the effect of famotidine in preventing weight gain induced by the olanzapine in patients with schizophrenia with more samples and a longer time.

MATERIAL AND METHODS

Trial design

This trial was a double-blind, parallel-group, placebo- and active-controlled study that was conducted during April 2015 to December 2015.

Participants

The study was performed on schizophrenic patients hospitalized in the psychiatric ward of the Golestan Hospital Medical Center. Golestan hospital is located in Ahvaz, Khuzestan, Iran and its psychiatric ward are one of the largest psychiatric centers in the country and the only referral center in southwestern Iran. The participants included 44 patients with schizophrenia (based on criteria of DSM-IV-TR.[13] at ages 20 to 55, treated with olanzapine treatment (in the range of the therapeutic dose).

Selection criteria

The 20 to 55- year patients suffering from schizophrenia (based on criteria of DSM-IV-TR), who recently started the olanzapine medication, were included in this study. In addition, we excluded the pregnant patients, people with a history of disease increasing weight (e.g., diabetes and hypothyroidism), a serious and chronic medical disorders, concomitant use of weight-enhancing drugs (except olanzapine) and patients with a BMI higher than 30 and patients with olanzapine discontinuation for any reason during treatment.

Interventions

Schizophrenia inpatients treated by the standard treatment of schizophrenia recently and based on indications of current clinical practice in association with olanzapine, were included in this clinical trial.

Evaluation for inclusion and exclusion criteria were done by an expert psychiatrist. Eligible patients in the study were divided equally into two groups of 22 using blocked randomization method.

In the case group, patients were given famotidine (Shafa Pharmaceutical & Hygienic Co, Iran) at a dose of 40 mg daily at 8 am and the control group received placebo at 8 am daily. In terms of appearance and physical properties, the placebo was quite similar with features of the drug famotidine and was made by the Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences.

During the duration of the study, samples were treated with olanzapine and other standard treatments of disease based on the response to their needs and in this respect, the researchers were not involved in the dosage and frequency of administration of medications consumed by patients and only famotidine drug or placebo was added to treat each patient. During the study, all patients were given a normal and same diet. Also, during the study period, none of the patients had physical exercise and a special diet for weight loss.[12]

Outcomes

BMI, height and weight of patients, respectively, using a height gauge and a standard scale (Seca, USA), were measured by a nurse trained in the principles of anthropometric measurements and based on correct principles of anthropometric measurements. The nurse was blind to the objectives of the study treatment groups. All measurements were done for everyone at baseline and weeks 2,4,6 and 8 and 8 am and before food meal.[14] Also, all patients were evaluated in terms of side effects and tolerability.

Research ethics

Before the study, at first, the trial was confirmed in ethics committee of Ahvaz University of Medical Sciences (ajums. REC. 13930401) and then the trial was registered on the Iranian Registry of Clinical Trials with IRCT2015041521779N1 code. Also, in accordance with the provisions of the Treaty of Helsinki, before the start of the project the voluntary and informed consent was taken from all participants. Before conducting the clinical trial, it was approved by the ethics committee of Ahvaz University of Medical Sciences (ajums. REC IR. AJUMS. REC.1394.13) on 2015-03-14. As well as it was registered on February 3, 2016 on Iranian Registry of Clinical Trials (irct.ir) IRCT2015052022349N1 code. A written commitment from all patients before participating in the study were taken voluntarily and knowingly. The objectives and the benefits and possible complications of the study were explained for all the subjects in a simple language.

Statistical analysis

Descriptive statistical methods, such as mean and standard deviation, were used. Also, to examine differences between qualitative variables the Chi-Square test was used; and to examine differences between quantitative variables the independent sample T-test was used; and to test the difference between the quantitative variables of more than two groups, one-way Anova test was used.

RESULTS

In this study, out of 44 groups in two patient groups. The first group received olanzapine and famotidine, and the second group received a placebo. Demographic data of patients are briefly given in table 1, and in terms of basic features, no significant differences were seen between the two groups at the beginning of the study.

Table1. Characteristics of the patients in Famotidine and Placebo groups at the baseline

Variable	Famotidine group (n=22)	Placebo group(n=22)
Age (year ± SD)	33.52±7.65	33.66±6.44
Gender(Male/ Female)	10/12	11/11
Weight(Mean ± SD)	65.41±7.96	66.31±5.33
BMI(Mean ± SD)	23.11±1.67	22.96±1.17

Results related to weight patients

The weighted average of patients in both groups had increased from start to eight weeks of treatment. This increase was not significant in the patients of the famotidine group ($P<0.05$). Although in the placebo group, weight changes were made significantly at the end of the study, compared to baseline. According to Table 2, the average weight of the two groups were different significantly, so that at the end of the study the weight gains occurred to a lesser extent in famotidine consumers compared with the placebo group ($P <0.0001$).

Results related to BMI patients

Similarly, the mean BMI of patients during treatment in both groups had increased from start to eight weeks. However, this increase was not significant in the patients who received famotidine ($P<0.05$). Although the change in BMI exhibited a significant increase in the placebo group at the end of the study compared with baseline. According to Table 2, the average BMI in the two groups was significantly different, as the increased BMI occurred to a lesser extent in the consumers of famotidine compared with the placebo group, at the end of the study ($P <0.0001$).

Famotidine was well tolerated by all patients and no side effects were reported in them.

Table 2. Characteristics of the patients in Famotidine and Placebo groups at the baseline and end line

Variable	Famotidine group (n=22)	Placebo group(n=22)	p-value
Weight (Mean ± SD)			
Baseline	65.41±7.96	66.31±5.33	<0.0001
Week 2	66.05±7.83	66.87±5.37	
Week 4	66.69±7.66	67.85±5.25	
Week 6	67.31±7.51	68.94±5.31	
Week 8	68.11±7.28	70.28±5.63	
p-value	0.78	0.03	
BMI (Mean ± SD)			
Baseline	23.11±1.67	22.96±1.17	<0.0001
Week 2	23.34±1.54	23.12±1.11	
Week 4	23.58±1.58	23.52±1.05	
Week 6	23.79±1.54	23.83±1.06	
Week 8	24.14±1.62	24.33±1.18	
p-value	0.1	0.001	

DISCUSSION

The increase in the standard rate of mortality in patients with mental disorders with natural and unnatural death is more related to the increased prevalence percentage of coronary heart disease (CHD) that is associated with obesity. Obesity is one of the most common problems in psychiatric patients that has been intensified recently due to the increased use of the second-generation antiepileptic drugs.[15, 16]

In different studies, the prevalence of obesity in patients with schizophrenia is 1.5 to 4 times more than the healthy population.[17, 18] The understanding of the prevalence of obesity in patients with mental disorders, which affect the patients ' deaths, is of special importance.[19] One factor that appears to be a potential role in the treatment of the side effects of weight gain in patients taking second-generation antipsychotic drugs, is famotidine. Famotidine is a histamine H2 receptor selective blocker, which inhibit gastric acid secretion and is used in general in the prevention and treatment of gastric and duodenal ulcers, gastroesophageal reflux disease and Zollinger-Ellison syndrome and also in the treatment of Alzheimer's disease and Parkinson.[20] Compared with other histamine H2 receptor selective blocker (H2 blockers), Famotidine has slightly fewer side effects and a little bit of drug interactions with cholinergic receptors, adrenergic receptors and histamine H1 receptor.[12]

The results of our study showed that However, the drug significantly over a period of eight weeks can lead to slow weight gain and BMI of schizophrenic patients who take simultaneously olanzapine. In other words, this drug has weight reducing properties. Famotidine and other H2 antagonists such as cimetidine and nizatidine, theoretically by inhibiting the histamine H2-receptor as one of the major systems involved in feeding behavior and the regulation of body weight, can reduce the weight of patients treated with the olanzapine.[8] However, the results of a meta-analysis study show that the majority of clinical trials conducted on the H2 antagonist drugs is incapable of the proving such a relationship.[21] Similarly, in the clinical trial conducted by Poyurovsky *et al.*[12] as the only clinical trial that investigated specifically the impact of famotidine in a combination with olanzapine in patients' weight gain, it was concluded that adding famotidine to olanzapine does not have an effect on reducing weight gain or preventing it. The result is quite contrary to the results of the study. The cause of the difference in the results of these two studies seems to be due to the small sample size and type 2 error arising in Poyurovsky *et al.*'s study as well as the shorter period of treatment in their study compared to our study (six weeks compared to eight weeks).

Furthermore, in a 16- week randomized double-blind clinical trial, Ranjbar *et al.* evaluated the effectiveness of ranitidine in preventing or reducing the amount of weight gain caused by olanzapine on 52 patients with schizophrenia. The results of this study suggest that administration of olanzapine- ranitidine mildly and slightly prevented the weight gain caused by the olanzapine in these patients.[22] In justifying these effects, the evidence showed that the ratio of H1 antagonists to H2 antagonists have a greater role in preventing the induction of weight gain caused by antipsychotic drugs. Furthermore, studies have shown that antibiotic drugs, such as olanzapine have more tended to apply their effect through the recipients. In addition, the mechanisms, except for the histaminergic mechanisms (such as 5H2C and beta adrenergic) are also involved in the incidence of weight gain.[12]

Similar to our study, in an 8-week double-blind randomized clinical trial, Cavazzoni *et al.* evaluated the effectiveness of nizatidine for treatment of olanzapine-induced weight gain in 175 patients with schizophrenia. The results showed that nizatidine significantly slowed down the process of weight gain in the *3rd* and *4th* weeks. However, at the end of 16 weeks, there was no difference between the consumers of nizatidine compared to placebo in this aspect. This indicates that nizatidine has temporary effect in preventing weight loss. Given

that the study was designed for 8 weeks we were not able to prove or refute the effect in famotidine.[23]

Moreover, in a 16-week clinical trial, the Lopez-Mato *et al.* investigated the effectiveness of the ranitidine to control the weight gain caused by the olanzapine in psychiatric patients. Similar to our study, Lopez Mato-*c et al.* showed that olanzapine without ranitidine causes an approximately 3.4 kg weight increase (an increase equivalent to 1.19 in BMI). On the other hand, in patients who received a dose of 600 mg of ranitidine, the curve of their gain weight was moving towards normality and showed an approximately 1.6 kg weight loss (an approximately 0.6 reduction in BMI). And in the end, they concluded that ranitidine is an effective drug in the prevention of weight gain caused by the olanzapine.[24]

Similar to the study conducted by Poyurovsky *et al.*[44], this drug was well tolerated and side effects was not report in any of the patients, and its safety and tolerability were confirmed.

CONCLUSIONS

Adding famotidine to the therapeutic process of olanzapine in patients with schizophrenia significantly causes preventing and reducing the effects of weight gain during the period of use in patients.

Suggestions

In order to continue the process of this study, persistence of specific studies is recommended for certain types of psychiatric illnesses as well as studies with multiple changes in therapeutic doses of medications to achieve the proper dosage suppressor weight gain.

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