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Original Article

A Randomized Double Blind Clinical Trial in Famotidine Adjuvant Therapy in Schizophrenia

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Abstract

Background: About 40%-60% of schizophrenic patients are resistant to ordinary treatment, which result from interference with different neurotransmitter systems in the process of disease. The aim of present study was to determine the effect of famotidine on several symptoms of schizophrenia which was nonresponsive to neuroleptic treatment.

Methods: 30 schizophrenic patients previously nonresponsive to ordinary treatment were categorized into two groups. Famotidine group received perphenazine plus famotidine and placebo group received perfenazine plus a placebo. Patients in both groups were followed for 6 weeks and assessed by the positive and negative symptom scales (PANSS) at weeks 0, 2 and 6 of the treatment.

Results: Both groups were similar in terms of positive and negative symptoms. In the placebo group, the total scores of PANSS (severity of the disease) did not change significantly. However, based on the total scores of PANSS, there was a significant difference between both famotidine and placebo groups at the end of sixth week ($P<0.05$). In terms of general psychopathology scale and aggressive risk, there was also a significant difference between both famotidine and control groups at the end of sixth week.

Conclusion: Famotidine can improve the symptoms of schizophrenic patients who were not responsive to neuroleptics.
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Keywords ● Famotidine ● H_2 receptor antagonists ● schizophrenia ● neuroleptics

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Introduction

Forty to sixty percent of schizophrenic patients show undesirable responses to available antipsychotic drugs.[1] Schizophrenic resistance to treatments with dopaminergic blocking drugs is thought to be due to changes of extradopaminergic systems such as histaminergic system.[2] Histamine has been suggested as a neurotransmitter, in the mammalian brain that regulates many brain functions.[2-5] The levels of histamine and its primary metabolites are higher in the cerebrospinal fluids of schizophrenic patients and is related to the recurrence and pro gression of the diseases.[6] There are many histamine H_2 receptors in various regions of the brain, including cortex, caudate nucleus, putamen, amygdala and

thalamus.[7] These regions play important roles in the pathology of schizophrenia.[8] In some researches, an increase has been shown for the density of histamine H_2 receptors in the lateral and internal parts of globus pallidus of schizophrenic patients.[9] The results of above studies suggest that histamine H_2 receptor antagonists should alleviate at least some of schizophrenia symptoms. Famotidine is a selective histamine H_2 receptor antagonists with an extensive use in digestive diseases. This drug has less side effects than other H_2 blockers and has shown less pharmaceutical intervention with cholinergic, adrenergic and histamine H_1 receptors.[10,11] In previous studies, famotidine with doses of 40 to 100 mg/day was prescribed for 5 to 18 schizophrenic patients and its efficacy was evaluated during 3 to 6 weeks without any control or placebo groups.[12-15] The purpose of this study was to determine the effect of famotidine on several symptoms of schizophrenia which were nonresponsive to neuroleptic treatment.

Patients and Methods

This study evaluated the randomized double blind, placebo-controlled clinical trial performed on 30 schizophrenic patients aged 18 to 45 years and non-responsive to antipsychotic drugs admitted to Zare psychiatric hospital, affiliated with Mazandaran University of Medical Sciences, Sari, Iran. The ethic committee of Mazandaran University of Medical Sciences has approved the study and accordingly a written informed consent was taken from each patient family. A non-responder was defined as a patient who had received at least two courses of classic antipsychotic drugs without positive response. All patients had a passing grade higher than 60 in the positive and negative indexes (PANSS). Exclusion criteria were pregnancy, any neurological or physical disorders, addiction to narcotic drugs and IQ score less than 70. Patients who had used sedative and hypnotic drugs, antidepressants and other mood stabilizers within last two weeks were also excluded. Patients were divided into two groups using a randomized list of medication codes. Famotidine or matching placebo tablets were prepared by Shafa Pharmaceutical Laboratory (Tehran, Iran) and dispensed in 10 tablet blisters. Patients were then randomly assigned to receive perphenazine/famotidine (40 mg/60 mg daily, n=15 males) or perphenazine /matching placebo (12 males and 3 females). For the prevention of extrapyramidal effects, biperiden (6 mg/day) was prescribed. Patients were visited during six weeks with the schedule of 0^{th}, 2^{nd} and 6^{th} weeks. Both famotidine and placebo groups were assessed by the positive and negative symptom scales (PANSS). Psychiatrists completed the PANSS questionnaire at the start of the study (baseline visit, week zero) and at the follow-up visits of 2^{nd} and 6^{th} weeks. Treatment assignments were not revealed to the study personnel, investigators, clinical staff, as well as study monitors until all patients completed the therapy and the database were finalized.

Statistical analysis

Analysis of quantitative data was done by repeated-measure analysis of variance (ANOVA), followed by Newman-Keuls as the *post hoc* test. The qualitative data were analyzed by Chi square method and the significant level was considered at $P<0.05$.

Table 1: Demographic characteristics of the patients of placebo and famotidine groups.

Variables		Placebo No (%)	Famotidine No (%)
Gender	Male	12 (80)	15 (100)
	Female	3 (20)	0
Occupation	Unemployed	15 (100)	15 (100)
Education	Illiterate	3 (20)	2 (13.3)
	Elementary	9 (60)	7 46.7)
	Secondary	2 (13.3)	3 (20)
	Higher	1 (6.7)	3 (20)
Familial backgrounds	Positive	4 (26.6)	3 (20)
	Negative	11 (73.4)	12 (80)
Type of schizophrenia	Paranoid	9 (60)	11 (73.3)
	Not paranoid	6 (40)	4 (26.7)
Hospitalization	Non	1 (6.6)	1 (6.6)
	Once	3 (20)	3 (20)
	2-4 times	4 (26.7)	4 (26.7)
	>4 times	7 (46.7)	7 (46.7)
Marital status	Unmarried	9 (60)	10 (66.7)
	Married	6 (40)	5 (33.3)

Results

The demographic characteristics of patients of the two groups presented were similar in (Table 1). Based on the total scores of PANSS, there was a significant difference between both famotidine and placebo groups at the end of sixth week ($P<0.05$). However in the placebo group, the total scores for weeks zero and 6 did not change significantly, indicating a resistant schizophrenia to classic antipsychotic treatments (Table 2). Treatment of placebo group reduced the positive and negative symptoms, but there was no significant difference between both groups at the end of the second and the sixth weeks. Side effects of the drugs were controlled during the treatment and only one patient of the famotidine group had urinary retention due to antimuscarinic effects of drugs and was excluded and replaced by another patient. Other patients tolerated the drugs and no

Table 2: The total scores (mean±SEM) from positive and negative symptom scales (PANSS) questionnaire in placebo and famotidine groups.

	Total scores		
Groups	**Zero week**	**2nd week**	**6th week**
Placebo	118.6 ± 8.1	106 ± 7.7	92.2 ± 7.1
Famotidien	132.6 ± 9.2	107 ± 7.9*	68.2 ± 6.4#§

*P<0.05, #P<0.001, different from the Famotide group at the zero week.
§P<0.05, different from the placebo group at the 6th week.

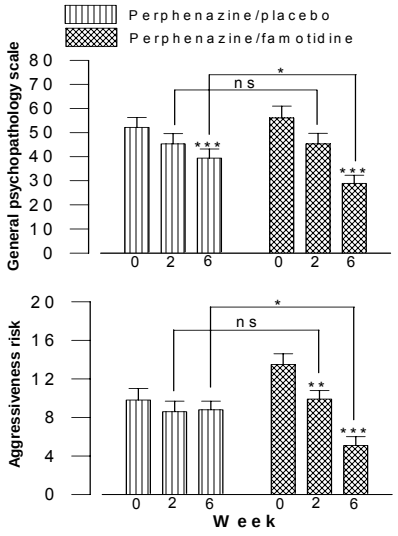

Fig 1. Measures of scores at weeks zero,2 and 6. Results are expressed as mean±SEM. *P<0.05, **P< 0.01, ***P< 0.001, different from control groups (ns=not significant).

serious adverse event was found to be related to the medication. Compared with placebo group, the means of general psychopathology scales and aggressive risks were lower in the famotidine group at the end of 6th week (Fig. 1, p<0.001). However, according to the general psychopathology scales, the aggressive risk were significantly lower in placebo group at the end of 6th week (Fig. 1, p<0.001).

Discussion

This study demonstrated that a 40 mg/day perphenazine combined with 60 mg/day famotidine is an effective and well-tolerated medication for the treatment of non-responsive schizophrenia compared with classic antipsychotic drugs. As a supplementary treatment, the prescription of famotidine to schizophrenic patients decreased the general psychopathology scale and aggressiveness risk scores of PANSS at the end of 6th week. Comparison of the mean of the total scores of PANSS between famotidine and placebo groups also indicated a significant difference at the end of 6th week. Thus, it seems likely that the overall benefit of perphenazine/famotidine treatment is clinically meaningful. The results of present study is in agreement with previous investigations carried out by Dannon,[16] but differs from the study of Abhari et al.[17] Both aforementioned studies did not have any placebo control group. In the present study, the onset of perphenazine effect supplemented with famotidine was faster than perphenazine alone. This is in agreement with Dannon et al.[16] In another word, famotidine accelerates the initiation time of neuroleptic effect. A decrease in the positive and negative symptoms has been confirmed by the open clinical trials on the famotidine effectiveness in schizophrenia.[14,15,18] However, in the present study, the effect of famotidine on the aggressiveness risk was more dominant than other elements of PANSS. In the absence of adequate studies in connection with the effect of famotidine on aggressiveness risk, it is required to carry out further clinical trials on the aggressiveness risk in schizophrenic or other psychotic patients. In the present study, more than half of schizophrenic patients were paranoid. Therefore, one may speculate that the efficacy of famotidine is higher in the schizophrenia associated with paranoid. This hypothesis is in agreement with the results of Oyewami open clinical trial in 18 schizophrenic patients.[14] In this study, famotidine and perphenazine did not have an apparently important side effects and were relatively well tolerated. This was in agreement with the results reported elswhere.[17] With respect to this hypothesis which points to the role of histamine in the schizophrenia etiology, our double-blind clinical trial confirms the usefulness of histamine H_2 receptor antagonists in alleviation of schizophrenia symptoms.

Conclusion

The famotidine adjuvant therapy seems to alleviate the symptoms of schizophrenic patients who are not responding to neuroleptics drugs.

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