CASE REPORT

Famotidine as an Adjunct Treatment of Resistant Schizophrenia*

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Some patients suffering from schizophrenia fail to respond to or tolerate adequate doses of available antipsychotic medications. Thus, innovative pharmacotherapeutic approaches, such as augmentation strategies, play an important role in the management of these treatment-resistant patients. A recent case report suggested that the administration of famotidine to a patient suffering from schizophrenia with peptic ulcer disease was associated with improvement in the deficit symptoms of schizophrenia. Famotidine is a potent highly selective H^2 receptor antagonist which crosses the blood-brain barrier. Impressed by this finding, famotidine was prescribed to some of our treatment-resistant patients suffering from schizophrenia who demonstrated significant deficit symptoms of schizophrenia. The subjects were 12 (eight male, four female) treatment-resistant psychotic patients whose antipsychotic medications were augmented with famotidine in an open trial. They ranged in age from 21 to 48 years with a mean age of 32.75 years. Seven of the 12 subjects made significant improvement resulting in discharge from hospital. Paranoid disturbances as well as absence of comorbid substance use were predictors of good response to famotidine augmentation of the antipsychotic medications. The results implied that H^2 receptor activity in the brain might play a role in the pathogenesis of deficit syndromes in schizophrenia. Further studies of this strategy are recommended, since it may open a window of understanding of the negative (deficit) syndrome and its treatment.

Key Words: resistant schizophrenia, adjunctive treatment, famotidine

INTRODUCTION

The treatment of patients suffering from schizophrenia who experience minimal or no response to adequate doses of the conventional neuroleptics represents an enormous challenge to clinicians. These neuroleptic treatment-resistant patients constitute up to 25% of all patients suffering from schizophrenia (Davis et al 1980). The recent introduction of atypical antipsychotic agents such as clozapine and risperidone brought some hope for this population. However, in spite of these advances, clinicians still encounter patients suffering from schizophrenia who remain unwell. A preponderance of these individuals suffer from negative (deficit) symptoms which account for much of the morbidity and diminished quality of life associated with chronic forms of

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schizophrenia. In such situations clinicians embark on therapeutic trials of alternative strategies that usually involve the addition of other agents to the standard antipsychotic treatments. Only a few, if any, of such adjunctive treatment strategies are studied in a systematic fashion to support their ongoing usefulness in clinical practice. Adjunctive treatments can result in polypharmacy and therefore require careful monitoring to identify the benefit, if any, from them.

The aim of this project was to assess the usefulness of adding famotidine (pepcid), a highly selective H^2 receptor antagonist, to the treatment of neuroleptic treatment-resistant schizophrenic patients. Our interest in this strategy was derived from two main sources:

1. some of our patients on adequate trials of traditional or atypical neuroleptics still showed prominent negative symptoms even when their positive symptoms had abated, and acute extrapyramidal syndromes controlled; and
2. Kaminsky et al 1990 reported that the administration of 40 mg famotidine daily was associated with improvement in the deficit symptoms of schizophrenia.

METHODS

This was an open trial. Participants were recruited from the pool of patients suffering from schizophrenia who had been referred to the Clinical Evaluation Unit (CEU), at a provincial psychiatric hospital by their psychiatrists because of non-response to an adequate trial of neuroleptics. An adequate trial is defined as receiving at least an equivalent dose of 800 mg of chlorpromazine for at least six weeks. The diagnoses of all the patients in this study satisfied the DSM-III-R criteria (American Psychiatric Association 1987) as determined by the Structured Clinical Interview for DSM-III-R, SCID, (Spitzer et al 1990) and consensus of the authors. As well, all patients' medications were reviewed to eliminate unnecessary polypharmacy, manage side effects and maximize benefits.

The clinical response of the patients was monitored with weekly assessments using the Nurses' Observation Scale for Inpatient Evaluation, (NOSIE), (Honigfeld et al 1966). Changes were also assessed with the Global Assessment of Function,(GAF) score (American Psychiatric Association, 1987) and the Clinical Global Impression (CGI), for severity of illness, (Guy 1976) on admission and at discharge or transfer from the unit.

The NOSIE scale has 30 items and uses a five-point scale on each item (1 = never; 5 = always) for a minimum score of 30 and a maximum score of 150. The CGI scale reflects overall severity of illness on a seven-point scale (1 = normal; 7 = among the most severely ill). The GAF scale reflects overall illness and level of function on a zero to 100 scale with 90 to 100 being normal and zero to ten indicating extreme incapacity requiring constant supervision.

The patients included in this report were those given an adequate trial of the traditional neuroleptics, clozapine or risperidone, with partial or total improvement of the positive symptoms but persistent (negative) deficit symptoms such as affective blunting, poverty of speech, low social drive, social inattentiveness and impaired grooming and hygiene (Andreasen 1987). Any acute extrapyramidal side effects were controlled. They were informed of the reasons of why 20 mg of famotidine would be added twice a day to their treatment, and they gave consent. Five patients who were on treatment for abdominal discomfort were given 20 mg of famotidine twice a day instead of their other stomach medications. Once initiated, the adjunctive treatment with 20 mg of famotidine, twice daily was continued for at least six weeks without alteration in the dose of the primary medications. Sociodemographic and clinical data on all participants were extracted from the CEU data base or case files.

The effect of the adjunctive treatment with famotidine on clinical outcome was determined by the change in the GAF, CGI (severity of illness) and NOSIE scores during the treatment. The effect on the positive and negative schizophrenic symptoms was assessed using the subscales of the NOSIE. The NOSIE consists of seven subscales: (social) competence, (social) interest, neatness, irritability, psychosis, retardation and depression. The NOSIE was designed as a treatment sensitive ward behaviour scale (Honigfeld et al 1966). The inter-rater reliability, factor structure and predictive validity of NOSIE in chronic patients suffering from schizophrenia has been well studied (Philip 1977, Dingemans et al 1984, Hafkenscheid 1991). We selected the NOSIE scale for this measure because it is completed every week by the nurses on all CEIJ patients. The interrater reliability was high between the nurses ($r = 0.91$, $p < 0.001$). However, most of the nurses were unaware of the expected outcome of the strategy, which eliminated some of the observer bias in open trials.

One-way analysis of variance was used to assess whether or not these measures were significantly different between the two groups.

RESULTS

Description of sample

Table 1 provides some background information on the 12 patients who participated in the study. There were eight males and four females. The mean age was 32.75 years (ranging from 21 to 48 years). Seven of them gave a past history of substance abuse. All were never married except for one woman who was divorced. The antipsychotic medications to which 20 mg of famotidine bid was added included both traditional neuroleptics, clozapine and risperidone. The combination was well tolerated. Although all were referred by their psychiatrists with diagnoses of schizophrenia, two were rediagnosed on the CEU as having delusional paranoid disorder and schizoaffective disorder, respectively. The mean age of onset of psychiatric illness for the group was 22.91 ± 7.75 years, and the average duration of psychiatric

Table 1

Sociodemographic and clinical description of population

Patients	Age	Sex	History of drug abuse	Medication before famotidine	Responder	CEU diagnosis
1	35	m	yes	risperidone 4 mg, BID; chloral hydrate 1 gm, hs	no	disorganized schizophrenia
2	26	m	no	sertraline 250 mg, od	yes	schizoaffective disorder (paranoid)
3	21	m	yes	risperidone 3 mg, BID	no	disorganized schizophrenia
4	27	m	yes	clozapine 350 mg, BID	yes	paranoid schizophrenia
5	32	m	no	clozapine 125 mg, hs	yes	paranoid schizophrenia
6	45	f	no	flupenthixol decanoate 10% solution 60 mg, im, q2wks	yes	delusional paranoid disorder
7	27	m	yes	clozapine 100 mg, qam, 400 mg, hs; clonazepam 0.5 mg, hs	no	disorganized schizophrenia
8	35	f	yes	flupenthixol decanoate 10% solution 60 mg, im, q2wks; lorazepam 1 mg, hs	no	disorganized schizophrenia
9	26	m	yes	flupenthixol decanoate 10% solution 50 mg, im, q2wks; fluoxitene 40 mg, BID	no	disorganized schizophrenia
10	48	f	no	haloperidol decanoate 125 mg, im, q2wks; carbamazepine 200 mg, BID	yes	paranoid schizophrenia
11	38	m	no	fluphenazine decanoate 18.75 mg, i.m., q2wks; procyclidine 5 mg, BID	yes	paranoid schizophrenia
12	34	f	no	clozapine 150 mg, q12h	yes	disorganized schizophrenia

illness was 9.58 years (range = two to 21 years). All were unemployed.

Before the addition of famotidine, all patients were assessed as markedly to severely ill (mean CGI, severity of illness score of 5.50 ± 1.0) and were unable to function in almost all areas (current GAF score of 26.25 ± 5.29). They stayed in bed most of the time, attended minimal or no program and kept to themselves. As a group the total NOSIE score was 77.8 ± 17.2.

Clinical response

All 12 patients showed marked improvement in their motivation and program participation levels within two to three weeks of adding famotidine to their treatment. There were significant changes from week zero to week six of treatment on the following measures: total NOSIE score 77.78 ± 17.23 *versus* 65.67 ± 14.05; $p = 0.001$, the NOSIE (negative score) 55.56 ± 11.63 *versus* 46.89 ± 11.88, $p < 0.001$, the current GAF score 26.25 ± 5.29 *versus* 66.40 ± 16.79, $p < 0.001$ and the CGI score 5.5 ± 1 *versus* 2.8 ± 1.48; $p < 0.001$. In some patients however, the improvement at week six was not sufficient to discharge them from hospital.

Responders *versus* non-responders

Responders were those who were assessed as ready for discharge by the treatment team or were already discharged by the end of the sixth week of the trial. In addition they were required to have obtained a CGI (severity of illness) score of three or less.

Seven of the 12 patients improved significantly enough to be discharged from hospital. Some sociodemographic and clinical factors differentiated the responders from non-responders. Responders were older (35.57 ± 8.541 years) than the non-responders (28.8 ± 6.10). There was no significant difference between both groups in terms of the average

Table 2

Outcome measures

Variable	Week zero	Week six/discharge	p-value
GAF score (current) (mean ± sd)			
• responders	28.71 ± 4.46	75.83 ± 8.61	< 0.001
• non-responders	22.80 ± 4.66	52.25 ± 16.64	0.39 (ns)
CGI (severity of illness) (mean ± sd)			
• responders	5.14 ± 1.07	2.33 ± 0.82	< 0.001
• non-responders	6.00 ± 0.71	3.50 ± 2.08	0.135 (ns)
Total NOSIE score (mean ± sd)*			
• responders	70.60 ± 17.65	56.50 ± 5.93	0.005
• non-responders	86.75 ± 14.43	75.50 ± 5.45	0.126 (ns)
"Negative" subscales (NOSIE)			
• responders	50.40 ± 11.76	40.40 ± 11.55	< 0.001
• non-responders	62.00 ± 8.76	55.00 ± 6.38	0.098 (ns)
"Positive" subscales (NOSIE)			
• responders	18.00 ± 7.00	15.20 ± 3.35	0.206 (ns)
• non-responders	22.00 ± 7.62	18.00 ± 5.72	0.375 (ns)

*Total NOSIE score did not equal the addition of negative subscales and positive subscales because the depression subscale was not treated as either positive or negative.

duration of illness (p = 0.943), however, responders were older at the onset of their illness (25.429 ± 9.449 *versus* 19.40 ± 2.19 years; p = 0.096). Gender, marital status, season of birth and family history of mental illness did not distinguish between the two groups.

When patients entered the study, there were no significant differences between responders and non-responders on measures of Current Global Assessment of Functioning (28.71 ± 4.46 *versus* 22.8 ± 4.66), the Clinical Global Impression score for severity of illness, (5.14 ± 1.07 *versus* 6.00 ± 0.7) and the total score on the NOSIE scale (70.60 ± 17.10 *versus* 86.75 ± 14.43). Thus both groups were severely ill and poorly functional.

A history of substance abuse was more prevalent among non-responders than responders, p < 0.013. All the five non-responders indicated a past history of substance abuse compared with only two of seven responders. After the evaluation on the CEU, all but one of the responders had a diagnosis of paranoid psychosis (four patients suffering from schizophrenia, one schizoaffective patient and one patient suffering from delusional disorder) while all but one of the non-responders were diagnosed as having schizophrenia disorganized type.

Effect on (negative) deficit symptoms

We used the scores on the subscales of the NOSIE scale to determine the effect of the augmentation strategy on the (negative) deficit symptoms in the population studied. Three of the seven subscales of the NOSIE scale measured some aspects of the (negative) deficit symptoms: (social competence, social interest and neatness) while three others; (irritability, psychosis and retardation) measured the positive symptoms. The depression subscale was excluded from this breakdown since it was negligible for both groups and did not change during the period of treatment (Table 2).

When the scores of the NOSIE subscales at week zero were compared with those at week six, there was statistically significant improvement in the negative subscales at discharge for the responders (p = 0.005), however, this was not statistically significant for the group of non-responders. The positive symptoms did not change significantly in either group.

DISCUSSION

The open trial design limits the assumptions we can make from the findings of this study, however the results further substantiated the earlier report by Kaminsky et al, (1990),

that famotidine is beneficial in the treatment of negative (deficit) schizophrenia.

All patients in this study showed marked improvement in their motivation level, participation in program and time spent out in the day room. Indeed, those who remained hospitalized (i.e., described as non responders by our definition) became more seclusive when famotidine was withdrawn from their treatment.

Both responders and non-responders improved somewhat and some of the change which was in common between the groups may be attributed to the ward milieu and the attention provided, but the alteration in social behaviour of the responders was more than can be attributed to such factors. It is also possible that there was an effect of the famotidine in the non-responders, but not enough to procure the degree of improvement needed for classification as a responder (i.e., readiness for discharge at end of six weeks).

The improvement in the deficit symptoms of social withdrawal, low social drive, poverty of speech and impaired grooming and hygiene shown by the patients was quite fascinating. In keeping with the findings of Kaminsky et al (1990), the clinical team was impressed to see the patients become more sociable, verbal and active within two to three weeks of initiating therapy with famotidine. Responders improved to the extent that they attended various activation and rehabilitative work program. Their social interaction with staff and peers improved. Indeed, antipsychotic medication was discontinued in one patient (11) (see Table 1) who was sensitive to neuroleptic side-effects. He was maintained successfully on 20 mg bid famotidine.

The data suggests that the responders were patients with paranoid disturbances who did not also have substance use disorder. Meltzer et al (1989) found the paranoid disturbance score of the Brief Psychiatric Rating Scale to be the single statistically significant predictor of drug response. Honigfeld and Patin (1989) also found an association between paranoid subtype diagnosis and drug response. Nonetheless, the patients in this study had been unresponsive to adequate doses of antipsychotic drugs before famotidine treatment was initiated. The responders were older than non-responders at the onset of illness. This is in keeping with the diagnosis of paranoid types of illness and a recent finding of Pickar et al (1992) who reported a later age of onset among "superior responders" to clozapine. Our findings supported the view that the response to adjunctive treatment with famotidine was limited to the negative (deficit) symptoms. This was quite an important finding because deficit symptoms, which account for much of the morbidity and diminished quality of life of patients suffering from schizophrenia, respond poorly to the traditional neuroleptics. A more intriguing aspect of the finding was that the famotidine was effective in patients whose negative symptoms persisted in spite of treatment with clozapine.

It is disappointing, nevertheless, that the most "negative" cases, namely, the disorganized ones, failed to reach the criteria of being ready for discharge. This may be related to their higher initial score for psychopathology, even though the moderate amount of improvement shown in both groups was quite similar. What seems to have happened was that the change procured was enough to raise the slightly better functioning patients into our category of "responders".

Famotidine is a potent highly selective H^2 receptor antagonist, which penetrates the blood-brain barrier even after oral administration (Kagevi 1987). Pharmacologically, it has negligible activity at the muscarinic, nicotinic, adrenergic or H^1 receptors. Hence-potentially, it is relatively safe when combined with antipsychotic medications. None of the patients included in the study reported worsening of existing side effects or new ones related to famotidine. Indeed, those with abdominal discomfort reported relief of those symptoms.

Much of the current understanding of the neurochemistry of schizophrenia has been derived from our knowledge of the antipsychotic medications. In spite of the fact that the first antipsychotic medication, chlorpromazine, possesses strong anti-histaminic properties, it is surprising that the role of histamine in psychoses has been neglected for so long. Prell and Green (1986), reported that histamine serves as a neurotransmitter and neuromodulator in the brain. They also found high levels of H^2 receptor activity in some areas of the brain implicated in schizophrenia. White and Runbold (1988) in a recent review reported that H^2 receptors transmit primarily inhibitory signals. Stimulation of the H^2 receptors decreased spontaneous activity and exploratory behaviour in animals. These reports suggest that overactive H^2 receptor activity could theoretically contribute to the negative symptoms of schizophrenia.

One may argue that the observed improvement was due to the increased plasma concentration of the antipsychotic drugs rather than a bonafide action on H^2 receptors. We do not have enough data to refute this. However, in one patient where we measured plasma clozapine concentration, the addition of famotidine did not significantly increase plasma clozapine.

The current findings call for greater attention to the role of histaminic receptors in the negative (deficit) symptoms of schizophrenia. There is increasing evidence from systematic studies that there may be three or more syndromes in schizophrenia with different mechanisms and etiologies (Malmberg and David 1993). Hence there is a need to pursue leads, such as those we reported here, because they could assist with our understanding of schizophrenia. Further studies, particularly double-blind, well controlled studies of the adjunctive treatment of negative (deficit) symptoms of schizophrenia with famotidine are recommended . We believe that further studies may open a window of understanding of the negative (deficit) syndrome and its treatment. In the words of Kaminsky et al (1990) "Clues to the biological defects in schizophrenia are rare, and every lead should be explored".

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