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Short Communication

Role of ranitidine in negative symptoms of schizophrenia – An open label study

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ABSTRACT

In this open label study, 75 patients with a diagnosis of schizophrenia were randomized to three groups of 25 each, receiving 150 mg/day ranitidine, 300 mg/day ranitidine and receiving only olanzapine. They were rated on PANSS at baseline, 4 and 8 weeks. There was a significant reduction in the scores of negative scale in patients receiving 300 mg/day ranitidine in comparison to patients not receiving ranitidine at the end of 4 weeks but was not seen again when assessed at the end of 8 weeks. Though effective in reducing the negative symptoms, the effect was not sustained due to the tolerance to the actions of ranitidine.

1. Introduction

Schizophrenia is a chronic, disabling brain disorder that affects some 1% of the population worldwide. The symptoms of schizophrenia can be divided into a group of positive symptoms e.g., hallucinations and delusions and negative symptoms. Negative symptoms can be considered to be the loss or reduction of certain normal functions or behaviours. The 2005 NIMH-supported consensus meeting, identified five subdomains of negative symptoms namely alogia, blunted affect, asociality, anhedonia, and avolition (Kirkpatrick. et al., 2006). They are the core components of schizophrenia that may improve in some cases with medications (Lecrubrier et al., 2006), but that unfortunately remain largely recalcitrant to current treatments (Erhart et al., 2006). The antidopaminergic drugs which are the mainstay of treatment, are usually effective against positive symptoms but not against negative symptoms (Burton, 2006; Lewis et al., 2006). This lack of effective treatment for negative symptoms is a particular problem because these symptoms impart a poorer outcome and prove to be most distressing for family members (Milev et al., 2005).

Numerous new approaches have been tried for the treatment of negative symptoms with H2 blockers being one of them. The first report on efficacy of H2 blockers appeared in the work of Kaminsky et al. (1989) who reported a dramatic improvement after famotidine was administered to a 36 year-old patient with schizophrenia. Subsequently, Deutsch et al. (1993) gave famotidine (40 mg/day) for 3 weeks in an open trial to ten patients with schizophrenia and found significantly lower scores on the Brief Psychiatric Rating Scale (BPRS) with a trend towards lower scores on the Scale for the Assessment of Negative Symptoms (SANS) during the study period. Another open label study highlighted the subjective improvement in both positive and negative symptoms after the addition of famotidine (100 mg/day) to a stable neuroleptic regimen (Rosse et al., 1996). There is just one placebo, controlled double blind open labelled study which failed to find a significant change in the negative symptoms of patients with treatment resistant schizophrenia on Tab. Famotidine (200 mg/day) for a period of four weeks (Meskanen et al., 2013).

Ranitidine is a nonimidazole H2 blocker which has a longer duration of action with greater 24 h acid suppression (Katzung, 2007). It has a negligible effect on muscarinic, nicotinic, adrenergic and H1 receptors. After oral administration, the absorption of ranitidine is rapid, with peak plasma concentrations occurring at 1–3 h. The peak plasma concentrations bear a constant relationship to dose, but vary widely between individuals (Roberts, 1984). It penetrates very poorly in the cerebrospinal fluid and the K_P, brain value in rats has been found to be less than 1 which is used for compounds having a poor CNS distribution (Kalvass et al., 2007).

This study was a part of another trial which was designed to assess the efficacy of ranitidine in olanzapine induced weight gain. Since, no effective treatments have yet been available for the negative symptoms, and with the lack of conclusive findings on the

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use of H2 blockers in the alleviation of negative symptoms, we decided to report the findings of this study. A null hypothesis was considered i.e., Ranitidine would have no role in the treatment of negative symptoms of schizophrenia when assessed on the Positive and Negative Symptom Scale for Schizophrenia (PANSS).

2. Methods

2.1. Setting

This was a hospital-based study conducted at Central Institute of Psychiatry, Ranchi, India.

2.2. Procedure

The study was conducted after obtaining the permission by the institutional review board and the trial was registered with the Clinical Trial Registry Of India (CTRI/2014/07/004740). Seventy five patients of either sex between 18 and 60 years of age fulfilling ICD-10 DCR (1993) criteria for schizophrenia giving informed consent were selected. All the patients were inpatients and diagnosed to have schizophrenia as their first episode. Those with any other major co-morbid psychiatric diagnosis and substance dependence excluding nicotine and caffeine, having significant medical or neurological illness and BMI >30 kg/m^2 were excluded from the study. They were then randomly allocated to 3 study groups using a randomization table by the investigating author comprising of twenty five patients each for study duration of eight weeks.

Study Group 1: The patients received Tab. Olanzapine and l50 mg of Tab. Ranitidine (low dose of Ranitidine) half hour before meals in the morning

Study Group 2: The patients received Tab. Olanzapine and 300 mg of Tab. Ranitidine (high dose of Ranitidine) as two divided doses before meals.

Study Group 3: The patients received Tab. Olanzapine only (no Ranitidine).

The patients belonging to all the study groups were given Tab. Olanzapine in the dose range of 10–40 mg depending upon the severity of illness. Administration of Tab. Trihexyphenidyl (2–6 mg/day) for extrapyramidal side effects (EPS) and Tab. Clonazepam (0.5–2 mg) for insomnia was allowed on as needed basis. The clinical assessment instruments were applied at baseline and at 4 and 8 weeks in all the three groups. These included the Positive and Negative Symptom Scale for Schizophrenia (PANSS) for assessment of positive and negative symptoms (Kay et al., 1987). This is a thirty item scale that is specifically developed to assess individuals with schizophrenia. The items are rated on a seven point continuum (1 = present, 7 = extreme). The assessment provides scores in nine clinical domains including a positive syndrome, a negative syndrome, depression, a composite index, and general psychopathology. The Udvalg for Kliniske Undersogelser (UKU) Side effect rating scale was also applied at 4 and 8 weeks for measurement of drug induced side effects (Lingjaerde et al., 1987). The randomization and all the clinical measurements were done by the investigating author as it was an open label study. All the patients continued to stay as inpatients for the study duration of 8 weeks after which Tab. Ranitidine was discontinued and olanzapine was adjusted/changed depending upon the severity of illness.

2.3. Analysis

The data was analyzed using descriptive statistics with the help of SPSS for Windows (version 16.0, Chicago, IL). Quantitative data was presented as mean (+SD). For the categorical variables, Chi square test was applied to analyze differences between the groups and Fischer's Exact test was computed for a 2×2 contingency table where the sample (N) was less than 20. The continuous variables were compared across the diagnostic groups using One Way Analysis of Variance (ANOVA) and the post hoc Bonferroni test. The results were considered significant at p value < 0.05.

3. Results

Socio-demographic and clinical characteristics of the sample have been summarized in Table 1. There was no difference

Table 1
Comparison of socio-demographic and clinical profile between the three groups.

Variables		Group 1 (N=25) Mean ± SD/n (%)	Group 2 (N=25) Mean ± SD/n (%)	Group 3 (N=25) Mean ± SD/n (%)	χ^2/F	df	p
Age (years)		31 ± 7.06	30.3 ± 7.36	32.2 ± 8.32	0.39	2, 72	0.68
Duration of illness (years)		4.63 ± 3.84	4.47 ± 2.98	6.04 ± 5.42	1.06	2, 72	0.35
Sex	Male	22 (88)	22 (88)	23 (92)	0.41*	2	1.00
	Female	3 (12)	3 (12)	2 (8)			
Marital Status	Married	14 (56)	17 (68)	14 (56)	1.00	2	0.73
	Unmarried	11 (44)	8 (32)	11 (44)			
Religion	Hindu	23 (92)	22 (88)	23 (92)	0.45*	2	1.00
	Islam	2 (8)	3 (12)	2 (8)			
Education	Upto 5th	7 (28)	2 (8)	3 (12)	4.26*	4	0.38
	6th–12th	14 (56)	16 (64)	15 (60)			
	Above 12th	4 (16)	7 (28)	7 (28)			
Occupation	Unskilled	14 (56)	7 (28)	13 (52)	5.28*	4	0.27
	Semiskilled	9 (36)	13 (52)	8 (32)			
	Skilled	2 (8)	5 (20)	4 (16)			
Socioeconomic status	Lower	10 (40)	10 (40)	6 (24)	1.89	2	0.42
	Middle	15 (60)	15 (60)	19 (76)			
Habitat	Rural	25 (100)	22 (88)	21 (84)	4.37*	2	0.15
	Urban	0 (0)	3 (12)	4 (16)			
Family history of psychiatric illness	Present	7 (28)	4 (16)	8 (32)	1.83	2	0.50
	Absent	18 (72)	21 (84)	17 (68)			
Family history of medical illness	Present	6 (24)	2 (8)	3 (12)	2.52*	2	0.35
	Absent	19 (76)	23 (92)	22 (88)			

* Fisher's exact test used

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