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EVALUATION OF EFFICACY AND SAFETY OF HIGH DOSE SECOND GENERATION NON - SEDATING ANTIHISTAMINES LEVOCETIRIZINE AND FEXOFENADINE IN CHRONIC URTICARIA - A PROSPECTIVE, PARALLEL, RANDOMIZED, SINGLE BLIND, COMPARATIVE STUDY.

Pharmacology

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ABSTRACT

There are few studies with up dosing of different 2nd generation antihistamines. This study evaluates efficacy and safety of high doses of Levocetirizine and Fexofenadine in chronic urticaria. This study includes 24 patients with chronic urticaria. Initially Fexofenadine 180 mg or Levocetirizine 5 mg was started. Doses of study drugs were doubled at the end of 1 week and tripled at the end of 2 weeks in non-responders and continued up to 4th week. Patients completed 2 week treatment with highest doses were included in the analysis. All patients were evaluated for symptoms, VAS for sedation and critical flicker fusion threshold (CFFT) for coordination before and after study. Reduction in mean total symptoms score and CFFT were highly significant in Fexofenadine group. Conclusion: Fexofenadine is superior to Levocetrizine in high doses in reducing mean symptoms score and sedation and no impairment in coordination in patients with chronic urticaria.

KEYWORDS

Chronic Urticaria, Second generation Antihistamines, CFFT, Sedation

Introduction:

Life time prevalence of urticaria is approximately 20% in general population. Urticaria is a heterogeneous group of diseases, having multiple underlying causes. Mostly it is idiopathic in nature. Chronic Urticaria (CU) is defined as daily presence of urticaria for at least 6 weeks without an identifiable cause. It may be acute and self limiting or chronic in some cases. These patients suffer from intense pruritus, associated with short lived, raised wheels, erythema with or without edema of deeper cutis [1, 2]. Chronic Urticaria is a distressing condition that severely affects the patient's quality of life and performance. Effective treatment is required in all most all cases, where avoidance of eliciting factors is not feasible [3]. The First line drugs recommended for chronic urticaria are second generation non-sedating antihistamines. In patients with inadequate control of symptoms with standard dose, an increased dosage of non- sedating antihistamines (NSAHs) up to 4 fold has been recommended [4]. This recommendation is based on the low cost, good safety profile and good evidence of efficacy of these drugs. The patients, who fail to respond to a 4 to 8 week trial of one second generation antihistamine, should switch to another second generation agent or to a first generation antihistamine, according to "Societe Francaise de Dermatologie (SFD) guidelines [5].

In India, few studies have been carried out with up dosing of different antihistamines in patients with chronic urticaria. These studies were conducted in small number of patients. Moreover, all are single armed and non randomized studies. Hence the present study is planned to evaluate the efficacy and safety of high doses of second generation antihistamines Levocetirizine and Fexofenadine in chronic urticaria.

Materials and Methods:

The study was conducted in the Dept of Clinical Pharmacology & Therapeutics, in collaboration with Dept of Dermatology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana state, India. It was a Prospective, parallel, randomized, single blind, comparative study. Study was started after Institutional ethics committee approval. Initially the participants were screened for eligibility into the study. Twenty four patients were included in the final analysis after obtaining informed informed consent. Inclusion criteria were Patients of either gender aged between 18 - 60 years with chronic idiopathic urticaria of duration of at least 3 months were enrolled into the study. Patients suffering from other forms of urticaria, patients with significant concomitant illness (malignancies, psychiatric, endocrine, hepatic or other major systemic diseases), pregnant women or lactating mothers, females on oral contraceptive pills and patients on antihistaminic therapy for 72 hours or steroids for one month were excluded from the study.

Methodology:

All the patients were investigated thoroughly to rule out any septic focus or any obvious cause of urticaria. The total leucocyte count (TLC), Differencial count (DC) and absolute Eosinophil count (AEC) were estimated in each patient at baseline and at the end of the study. At the initial visit, a detailed history was taken and general and systemic examination was conducted. Vital signs were measured. Baseline measurements of efficacy parameters were also measured. All patients were randomized either to fexofenadine 180 mg or levocetirizine 5mg, both the drugs given orally, once daily at bed time. Patients were monitored at weekly intervals, for 4 weeks. Patients who were responding to treatment had been continued with the same dose of the drug. In non responding patients, the dose of fexofenadine was doubled to 360 mg (2 tablets) in 2 divided doses at the end of 1 week and 540 mg (3 tablets) in 3 divided doses, at the end of 2 weeks and continued up to the end of 4th week. In the same way, the dose of levocetirizine was doubled to 10mg (2 tablets) at bed time, at the end of 1 week and 20mg (4 tablets) in 2 divided doses at the end of 2 weeks and continued till the end of the study (4th week). The evaluator was blinded to the treatments. The clinician incremented the doses of study drugs. Patients who completed 2 week treatment with higher doses of study drugs were included in the analysis.

All patients were evaluated for symptoms (degree of pruritus, number of wheals, size of wheals and number of individual urticarial episodes per week), visual analogue scale (VAS) for sedation and critical flicker fusion threshold (CFFT) for co ordination. Degree of pruritus was measured as 0 (None), 1 (mild), 2 (moderate), 3 (severe), Number of wheals as 0 (none), 1 (1- 10 wheals), 2 (11- 20), 3 (> 20 wheals), Size of wheals (Mean Diameter): 0 (No lesion), 1 (less than 1cm), 2 (less than 2.5cm), 3 (> 3cm) and number of separate urticarial episodes as 0 (No episodes), 1 (1 episode), 2 (2-3 episodes), 3 (> 3 episodes) per week. Maximum value of the total symptoms score (TSS) was 12 [6, 7]. Any change in the mean total symptom score was recorded before and after the study.

Visual analogue scale for sedation ranging from 0 - 100 mm, 0, no sedation and 100 extreme sedation. Sedation was graded as mild, moderate and severe. Critical flicker fusion threshold (CFFT) for assessing the Cognitive function and CNS arousal was recorded before and after the study. Adverse effects were recorded at each visit.

Critical flicker fusion Threshold (CFFT)

CFFT Instrument: This instrument is a Portable device, in house built LED based instrument. Monochromatic red LED light of wave length 630nm, fixed on white back ground is used as Flickering light source. On one side of apparatus there were dials to adjust the surrounding intensity, field intensity and flicker frequency.

Method of testing: Subjects were tested in a minimally illuminated room, with the CFFF measuring device kept at a distance of 30cm. Subjects were properly instructed, asked to respond by lifting the hand and tested by increasing and decreasing the frequencies. When the frequency is increased, at one point the flickering stops and light is perceived as a steady source (flicker to fusion). If the frequency is decreased from higher levels at one point flickering appears (fusion to flicker). Both ascending and descending frequencies were recorded and the mean of the two is taken as CFFT. Flicker to fusion and fusion to flicker was regarded as one cycle. Test was repeated for 3 cycles at an interval of 5 minutes. Mean of the 3 cycles was taken before and after the study.

Statistical Analysis:
Data was expressed as mean ± SE and categorical data in percentage. P value of < 0.05 was considered as statistically significant. Data within the groups was analyzed using paired student t test and between the groups by unpaired t test.

Results

In the present study, total 60 patients were screened. Twenty patients were screen failures and 40 patients were enrolled into the study. Out of 40 patients, five patients were lost to follow up, 4 patients withdrew from the study and 7 patients taken steroid injections in an outside hospital, during the study period. A total of 24 patients were included in the final analysis, 12 patients in Levocetrizine group and 12 patients in Fexofenadine group. Male patients were 14 and females were 12. Mean age of patients in Levocetirizine group was 28.55 ± 9.5 and in Fexofenadine group was 32.6 ± 8.9 years (Table - 1).

Table - 1 Demographic Characteristics

S No	Parameter	Fexofenadine Group (n = 12)	Levocetirizine Group (n = 12)
1	Mean age (yrs)	32.6 ± 8.9	28.55 ± 9.5
2	Males	8	7
3	Females	4	5

In Fexofenadine group the mean total symptoms score (sum of scores of degree of pruritus, number of wheels, size of wheels and number of separate urticarial episodes per week) before and after study was 10.1 ± 2.64 and 0.90 ± 1.1 respectively (Table - 2).

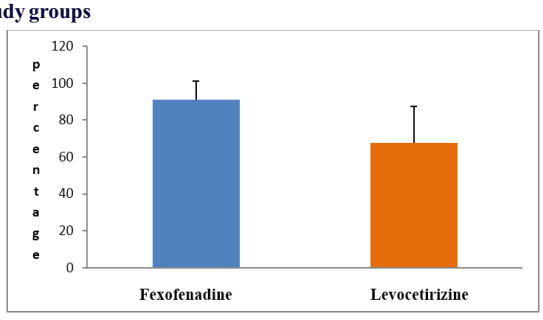
Table - 2 Efficacy parameters Before and After the study

S No	Parameter	Fexofenadine group		Levocetirizine group	
		Before	After	Before	After
1	The mean total Symptoms score	10.10 ± 2.64	0.90 ± 0.4 $	11.36 ± 1.5	3.82 ± 0.71 $
2	VAS score	23.8 ± 4.0	16 ± 4.0 **	13.4 ± 3.89	22.55 ± 3.22 **
3	Critical flicker fusion threshold (CFFT)	36.5± 2.9	33.4 ± 3.1 $	37.4 ± 2.6	402.53 $ .68 ±

$ - p<0.0001, ** - p< 0.001,

The mean total symptoms score before and after study in Levocetrizine group was 11.36 ± 1.5 and 3.82 ± 2.36 respectively. There was highly significant decrease (p < 000.1) in the mean total symptoms scores in both the study groups. The mean percentage (%) improvement in total symptoms score was 91.23 ± 10.1 in Fexofenadine group and was 67.84 ± 19.4 in Levocetirizine group at the end of study (Fig - 1).

Fig - 1 Mean Percentage improvement in symptoms scores in the study groups



The mean total symptoms score was significantly (p < 0.01) decreased, in Fexofenadine group when compared to Levocetirizine group (Table - 3). This showed that Fexofenadine decreased the symptoms score more effectively than that of Levocetirizine.

Table - 3 Comparison between study groups

S No	Parameter	Fexofenadine Group (n = 12)	Levocetirizine Group (n = 12)	P value
1	The mean total symptoms score	0.90 ± 0.4	3.82 ± 0.71	P < 0.01
2	VAS score	16 ± 4.0	22.55 ± 3.22	P = 0.2
3	CFFT	33.4 ± 3.1	40.68 ± 2.53	P < 0.0001

There was a highly significant (p < 0.0001) increase (8.7%) in critical flicker fusion threshold in Levocetirizine group when compared to baseline. It indicated impaired cognition and alertness in this group. In Fexofenadine group a highly significant (p < 0.0001) decrease (8.5%) was noted in CFFT compared to baseline denoting no impairment of cognition and alertness (Table - 2). The mean CFFT in Fexofenadine group was significantly (p < 0.0001) decreased, when compared to Levocetirizine group (Table-3). This showed that patients in Levocetirizine group showed more psychomotor impairment based on CFFT test compared to Fexofenadine group.

There was a significant (p < 0.001) increase in sedation on VAS scale in Levocetirizine group from the baseline to end of the study. In Fexofenadine group, a significant (P < 0.001) decrease in sedation on VAS scale was observed compared to baseline (Table - 2). The mean sedation score on VAS was not significant, when compared between the two study groups.

There were no side effects with increased doses of Fexofenadine. In Levocetirizine group at higher doses, sedation interfered with the daily activities in 2 subjects. No other side effects were observed in both the study groups.

Discussion

Patients with chronic urticaria who do not respond to licensed doses of non- sedating second generation antihistamines should be switched to higher doses (up to 4 fold) [1, 4, 8, 9] in order to obtain a better disease control, according to current recommendations. A number of studies demonstrated that many patients who were previously uncontrolled, showed significant improvement of their symptoms after following the above recommendation [8, 10]. They also indicated that these enhanced results have been accomplished without compromising patient's safety, since no increased rates of side effects have been reported, including somnolence [10]. The mechanisms explaining patient's benefits from up dosing are not completely understood, but increased in vivo receptor occupancy and effects of antihistamines on additional receptors have been proposed [11, 12].

Patients in this study were evaluated for degree of pruritus, size of wheals, number of wheals and number of separate urticarial episodes from the baseline to end of the study (one month). Efficacy measures were scored following a scale where maximum value of total symptom score (TSS) was 12. The mean percentage (%) improvement in total symptoms score was 67.84 ± 19.4 in Levocetirizine group and was 91.23 ± 10.1 in Fexofenadine group. In our study higher doses of Fexofenadine showed better objective improvements in symptom scores than levocetirizine. Our results are consistent with the previous studies [8, 13, 14, 15]. Finn et al [13] used a higher dose of 240 mg of Fexofenadine where as we had used 540 mg of fexofenadine (3 times of normal dose). The mean CFFT value in Fexofenadine group was significantly decreased, when compared to Levocetrizine group. This indicated that patients in Levocetirizine group showed more psychomotor impairment based on CFFT test compared to Fexofenadine group. The study conducted by Johnson et al [16] supported our results.

In our study Fexofenadine group showed decreased sedation on VAS scale where as Levocetirizine group showed increased sedation on VAS scale with higher doses. But there was no statistically significant difference in VAS score between the study groups. In contrast to our study, Staevska et al [9] in 23 patients reported that patients taking higher doses of levocetirizine (20mg QD) showed a paradoxical decrease in somnolence, which was attributed to the relief from urticaria related discomfort leading to a better quality of sleep. An

alternative explanation would be development of tolerance to the central nervous sedative effects of the antihistamines.

In the literature, headache was the most frequent adverse effect reported for Fexofinadine. But in our study no patient had complained of head ache.

In Conclusion, Fexofenadine in higher doses, showed better improvement in symptoms score and no psychomotor impairment, when compared to Levocetirizine. This supports the recommendation that increased doses of non - sedating antihistamines showed improved efficacy in patients with chronic urticaria who do not respond to approved doses. But additional studies are required using more number of patients.

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