

EFFICACY AND SAFETY OF BEPOTASTINE, A NEWER 2ND GENERATION ANTIHISTAMINE, COMPARED TO FEXOFENADINE IN ALLERGIC RHINITIS***¹Dr. Swapnil Deshmukh, ²Dr. Varsha Narayanan and ³Dr. Amit Bhargava**¹MBBS, MD, Manager, Medical services, Lupin Limited.²MBBS, MS, DGM, Medical services, Lupin Limited.³MBBS, MD, Vice president, Medical services, Lupin Limited.***Corresponding Author: Dr. Swapnil Deshmukh**

MBBS, MD, Manager, Medical services, Lupin Limited.

Article Received on 27/06/2018

Article Revised on 17/07/2018

Article Accepted on 07/08/2018

ABSTRACT

Background: Second-generation antihistamines are recommended as a first-line treatment option for adult allergic rhinitis (AR). Bepotastine is new oral selective H1 antihistamine. This study was done to evaluate comparative efficacy and safety of bepotastine with fexofenadine. **Material and methods:** This was a phase III, multicenter randomized double blind, prospective comparative study in 239 patients with AR. Patients were divided into two groups receiving either Bepotastine 10 mg tablets or Fexofenadine 60 mg capsule twice daily for 4 weeks. Change in Total symptom score (TSS), Total nasal symptom score (TNSS), Total ocular symptom score (TOSS), Rhinoconjunctivitis quality of life (RQOL), individual nasal & ocular symptom scores. Intergroup comparison was also done on TSS. Investigator's & patients' global assessment were also compared between two treatment groups. **Results:** After 4 weeks of treatment, both the groups showed statistically significant improvement in all the parameters like TOSS, TNSS, TSS, RQOL, individual nasal and ocular symptom score compared to baseline. Intergroup comparison did not show any statistically significant difference. Greater improvement from baseline score was seen in bepotastine group compared to fexofenadine (29.17±7.54 Vs 23.85±9.95) on six digit cancellation test score for assessing psychomotor performance, though the difference was not statistically significant. **Conclusion:** The trial concluded that bepotastine showed comparable efficacy to fexofenadine in the management of AR. Bepotastine caused less sedation and greater improvement in psychomotor performance. Both treatment groups demonstrated good safety profile.

KEYWORDS: Bepotastine, Fexofenadine, Allergic rhinitis.**INTRODUCTION**

Allergic rhinitis (AR) is a common IgE antigen and mast cell mediated allergic inflammatory disease, affecting 10% to 25% of people worldwide and up to 40% of the population of some countries.^[1,2] The disease is characterized by sneezing, congestion, rhinorrhea and nasal or palatal itching. Nasal congestion is the predominant manifestation of AR^[3] and is considered by patients to be the most troublesome symptom.^[4] AR may also coexist with allergic conjunctivitis associated with itching, watery red and swollen eyes. Oral antihistamines are generally viewed as being more effective in controlling the nasal itching, sneezing, and rhinorrhea associated with AR than in relieving nasal congestion.^[5-8] It is well known that first generation antihistamines such as chlorpheniramine and diphenhydramine while relieving allergic symptoms can also cause CNS related side effects such as sedation & psychomotor impairment. Oral Bepotastine, a newer second generation H1 receptor antagonist that also suppresses some allergic

inflammatory processes is indicated in treatment of AR, urticaria & pruritus associated with skin diseases in several Asian countries. It is found that Bepotastine has very low liability to produce sedative effect at therapeutic doses.^[9] Fexofenadine is a commonly used oral antihistamine for AR. There are no published trials directly comparing efficacy and safety of Bepotastine to Fexofenadine in AR patients.

MATERIAL AND METHODS

This was a phase III, multicenter randomized double blind prospective comparative study. A total of 239 patients with AR were enrolled in the study, out of these 203 completed the study and were considered for final analysis. Patients were divided into two groups receiving either Bepotastine 10 mg tablets or Fexofenadine 60 mg capsule twice daily for maximum period of 4 weeks. The treatment period varied from 10-28 days depending upon time required to resolve the symptoms. Male and Female patients, aged 18 to 65 years with Total Nasal Symptom

Score (TNSS) of 6 or greater or Total Ocular Symptom Score (TOSS) of 4 or greater were included in the study. Patients with known history of hypersensitivity to the study drugs, pregnant & lactating females, those who were already on any other medications and patients with deranged liver and kidney functions were excluded from the study. Total 30 patients of both groups failed to match inclusion criteria. Primary efficacy variable of the study was Total Symptom Score (TSS) (Combination of TNSS & TOSS) at the end of study compared to baseline. Primary safety variables are change in the laboratory parameters and occurrence of ADRs.

Change in TSS, TNSS, TOSS, Rhino-conjunctivitis quality of life (RQOL),^[10] individual nasal & ocular symptom scores as well as mean change in the six digit cancellation test for psychomotor performance score at the end of study were compared to baseline. Change in the TSS were also compared between the groups.

Statistical analysis was carried out using two tailed t test assuming unequal variance. All statistical tests were performed at 5% level of significance. Investigator's & patients' global assessment were compared between two treatment groups using Mann Whitney-Wilcoxon test or t test.

RESULTS

In this study total 119 patients were enrolled in the Bepotastine group out of which 72 were males and 47 were females & total 120 patients were enrolled into Fexofenadine group including 69 males and 51 female patients. Average age of Bepotastine group was found as 35.31 years whereas Fexofenadine group had average patient age of 32.23 years.

The comparative efficacy of the two drugs were assessed on total nasal symptom score (TNSS) [Table no. 1; Graph no. 1], Total ocular symptom score (TOSS) [Table no.2;Graph no. 2] as well as on quality of life [Table no. 3].

Table No. 1: Effect on Total nasal symptom score (TNSS) - Bepotastine vs Fexofenadine.

TNSS	Bepotastine (n=103)	Fexofenadine(n=100)
Before treatment(Mean±SD)	6.66±1.33	6.82±1.11
After treatment(Mean±SD)	1.44±1.67	1.50 ±1.73
Mean difference (Mean±SD)	5.22±0.34	5.32±0.62
P value for before treatment vs after treatment	P<0.05	P<0.05
P value for Bepotastine vs Fexofenadine at End of Treatment	p>0.05	

The decrease in score before and after treatment was statistically significant in both groups. The mean individual nasal symptom score decreased significantly after the treatment with Bepotastine or Fexofenadine as

seen in table no. 2. But when both treatment groups were compared the difference between the groups was not statistically significant.



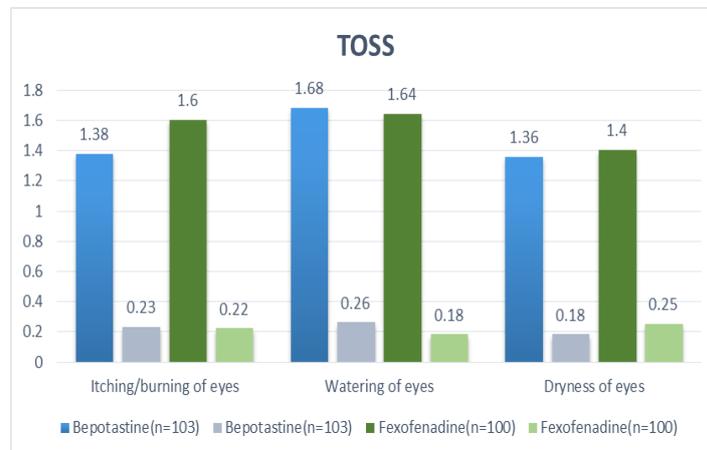
Graph No. 1: Effect on individual Total nasal symptom score (TNSS) parameters - Bepotastine vs Fexofenadine.

There was significant improvement in TOSS parameters after treatment with both Bepotastine and Fexofenadine.

However there was no statistically significant difference between the two groups. [Table no. 3, 4].

Table No. 2: Effect on Total ocular symptom score (TOSS) - Bepotastine vs Fexofenadine.

TOSS	Bepotastine (n=103)	Fexofenadine(n=100)
Before treatment(Mean±SD)	4.41±0.76	4.64±0.81
After treatment(Mean±SD)	0.69±1.10	0.65±1.01
Mean difference (Mean±SD)	3.72±0.34	3.99±0.20
P value for before treatment vs after treatment	P<0.05	P<0.05
P value for Bepotastine vs Fexofenadine at End of Treatment	p>0.05	

**Graph No. 2: Effect on individual Total ocular symptom score (TOSS) parameters - Bepotastine vs Fexofenadine.****Table No. 3: Effect on total quality of life score (QOL).**

QOL	Bepotastine (n=103)	Fexofenadine(n=100)
Before treatment (Mean±SD)	16.85±7.69	18.38±7.09
After treatment (Mean±SD)	2.55±3.87	2.15±2.15
Mean difference (Mean±SD)	14.3±3.82	16.23±4.94
P value for before treatment vs after treatment	P<0.05	P<0.05
P value for Bepotastine vs Fexofenadine at End of Treatment	p>0.05	

Both the treatment group showed statistically significant decrease in the Quality of life scores (improvement in QOL), however the difference between the two groups was not statistically significant. (Table no. 3).

The effect of two drugs on sedation and psychomotor performance was also assessed by six digit cancellation test score. (Table no. 4).

Table No. 4: Effect of Bepotastine and Fexofenadine on sedation and psychomotor performance assessed by six digit cancellation test score.

Visits	Bepotastine (n=103)	Fexofenadine(n=100)
Screening (Visit 1,Day 1)	80.73(±36.16)	80.73(±36.16)
End of treatment visit (Day 10-28)	109.9(±28.62)	106(±23.84)
Change from baseline	29.17(±7.54)	23.85(±9.95)
P value for before treatment vs after treatment	P<0.05	P<0.05
P value for Bepotastine vs Fexofenadine at End of Treatment	p>0.05	

There was improvement in psychomotor performance and decrease in sedation at the end of the treatment as the patients were able to concentrate better due to improvement in the symptoms of Allergic rhinitis. Greater improvement was seen with Bepotastine but it did not reach statistical significance.

similar ratings in 87% of patients. Bepotastine treatment was rated as “very good” & “good” by 81.34% of patients and Fexofenadine treatment was given similar ratings by 83% of patients. Investigator’s and patient’s assessment about Bepotastine and Fexofenadine were comparable and no significant differences were observed.

Bepotastine treatment was assessed as “very good” and “good” by Global investigator’s assessment evaluation in 82.52% patients while Fexofenadine treatment had

No Adverse drug reactions were reported in both the groups. In all 203 patients who completed the trial both

Bepotastine and Fexofenadine was not found to affect blood counts, liver and renal function test.

DISCUSSION

The results of the present study indicated that the second-generation antihistamines bepotastine and fexofenadine were useful for relieving the morning symptoms of allergic rhinitis. Previous phase 3 study has compared Bepotastine with Terfenadine in Allergic Rhinitis, as detailed further. Fexofenadine is a metabolite of Terfenadine and commonly used in the management of AR. To our knowledge this is the first study directly comparing Bepotastine to Fexofenadine in AR.

Oral Bepotastine is a highly selective second-generation histamine H1 receptor antagonist and has shown long-lasting, dose-dependent antihistaminic and antiallergic activity *in vitro* and *in vivo*^[11]. In addition, Bepotastine has been seen to exhibit mast cell stabilization and Leukotriene B4 inhibition which contribute to its anti-pruritic and anti-inflammatory actions. Bepotastine decreases Platelet activating factor (PAF) and antigen induced eosinophilic infiltration, as well as suppresses production of pro-inflammatory cytokines like interleukin-5 and interleukin-1a. It also acts to suppress nitric oxide production in vascular endothelial cells, which may lead to suppression of itch induced by substance P. Bepotastine's action on inhibition of intercellular adhesion molecule-1 (ICAM-1) expression in human epidermal keratinocytes and vascular endothelial cells decreases recruitment and infiltration of inflammatory cells.^[11]

Bepotastine is rapidly absorbed after oral administration with onset of action within half hour and T max of 1.2 hours.^[12] Its pharmacokinetics is not significantly affected by food. It shows a 55% blood protein binding with minimal hepatic metabolism which is not CYP dependent. Elimination half life is 2.4 hours with 80% oral Bepotastine excreted in urine unchanged. Bepotastine does not appear to accumulate in the body due to stable elimination half life with repeated dosing.

Brain penetration of Bepotastine is restricted by P-glycoprotein (P-gp) which makes it a non-sedating antihistamine.^[13] However due to high membrane permeability, and absorption of Bepotastine in the upper small intestine, (where P-gp expression is minimal), almost complete absorption takes place unaffected by intestinal P-gp.

Short- and long-term clinical and post marketing studies have shown 10mg twice-daily Bepotastine to be effective and well tolerated in the treatment of allergic rhinitis. A phase III comparative clinical trial comparing bepotastine with terfenadine in patients of perennial allergic rhinitis has shown better efficacy of bepotastine in controlling nasal symptoms like paroxysmal sneeze, nasal discharge, nasal obstruction, impairment of everyday activities and severity (59–70% of Bepotastine

group versus 49–60% of Terfenadine group). A significantly greater proportion of Bepotastine than Terfenadine recipients had utility ratings of useful or greater (61.2% vs 37.4%; $p = 0.001$).^[14] Our study findings also validated clinical efficacy of bepotastine. We found significant improvement in all parameters of TNSS and TOSS score from baseline and results were comparable to fexofenadine (tables & graphs no.1 & 2).

The phase III trial also reported that overall safety rating was better with Bepotastine than with Terfenadine in the comparative trial in patients with perennial allergic rhinitis however, differences between Bepotastine and Terfenadine in the proportion of patients with a rating of no problem with safety (90.7% vs 81.7%) was not significant ($p = 0.054$).^[14]

The efficacy of long term (24 weeks) Bepotastine 20mg/day treatment showed final global improvement rating of moderate or greater in 89.1% (95% CI 76.4, 96.4) with the proportion of patients with moderate or greater improvement relative to the control period increasing over time (37.8% at week 2 to 78.0% at week 12 and (80.8%, 76.9% and 100% at week 16, 20 and 24, respectively).^[15]

In post-marketing surveillance studies in children and adults with perennial and/or seasonal allergic rhinitis, efficacy ratings of satisfactory or almost satisfactory were reported by 89.5% of 1309 pediatric patients^[16] and 91.3% of 2766 adult and children respectively. The frequency and type of adverse events was not seen to increase with long-term use of Bepotastine with adverse events (most commonly drowsiness reported in 1.5%, falling to 0.7% in patients using Bepotastine for 4 weeks to 6 months).^[17] This study did not report any ADRs by bepotastine treatment which further validates the good safety profile of the drug as mentioned in previous studies.

A double-blind, placebo-controlled, comparative study of 473 pediatric PAR patients (7 - 15 years old) showed Bepotastine was superior to placebo in improvement of overall nasal symptoms of PAR compared with baseline values. No clinically significant adverse drug reactions often observed with first-generation antihistamines were reported and no difference in adverse events between groups was observed.^[18] In a recent study, Bepotastine was seen to suppress allergy-related symptoms without impairing work performance in subjects with seasonal allergic rhinitis caused by Japanese cedar pollen or cypress pollen.^[19]

A double-blind, placebo-controlled, crossover study to compare the inhibitory effects of Bepotastine (10 mg twice a day), Cetirizine (10 mg once a day), Fexofenadine (60 mg twice a day), and Olopatadine (5 mg twice a day) on histamine-induced flare-and-wheal response, also compared the sedative effects and impaired psychomotor activities by these drugs by a

visual analogue scale for subjective sedation, and by word processor test for psychomotor activity. Olopatadine, Fexofenadine, and Cetirizine showed a significant systemic sedative effect and affected psychomotor performance and in this order with Bepotastine showing the least sedative effect.^[20]

Our study has shown that Bepotastine has comparable efficacy and tolerance to Fexofenadine, a commonly prescribed antihistamine in AR, in improving both symptom scores and Quality of Life in Allergic Rhinitis patients.

CONCLUSION

Bepotastine is a newer 2nd generation nonsedative antihistamine which can be an effective treatment option for Allergic Rhinitis. Bepotastine has shown comparative efficacy and tolerance to Fexofenadine.

More comparative studies from other parts of the world geared to measure drug induced sedation and psychomotor impact along with improvement in symptom relief scores are warranted.

REFERENCES

1. Compalati E, Penagos M, Henley K, Canonica GW. Allergy prevalence survey by the World Allergy Organization. *Allergy Clin Immunol Int: J World Allergy Org.* 2007; 19: 82–90.
2. Sibbald B. Epidemiology of allergic rhinitis. In: Burr ML, ed. *Epidemiology of Clinical Allergy. Monographs in Allergy. Vol 31.* Basel, Switzerland: Karger; 1993; 61–79.
3. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: Development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol.* 1994; 93: 413–423.
4. Shedden A, Iezzoni D. Congestion and its impact on sleep in individuals with allergic rhinitis. Presented at: 25th Congress of the European Academy of Allergology and Clinical Immunology; June 10–14, 2006; Vienna, Austria.
5. Bousquet J, van Cauwenberge P, Khaltaev N, for the Aria Workshop Group and the World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001; 108(Suppl): S147–S334.
6. Bousquet J, Khaltaev N, Cruz AA, et al, for the World Health Organization, GA(2)LEN, and AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008; 63(Suppl 86): 8–160.
7. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) guidelines: Management of allergic rhinitis. *Prim Care Respir J.* 2006; 15: 58–70.
8. Dykewicz MS, Fineman S, Skoner DP, et al, for the American Academy of Allergy, Asthma, and Immunology. Diagnosis and management of rhinitis: Complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol.* 1998; 81: 478–518.
9. Kato M et al. Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. *Arzneimittelforschung.* 1997 Oct; 47(10): 1116-24.
10. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996; 98: 843-845.
11. ADIS drug profile: Oral Bepotastine in Allergic disorders. *Drugs* 2010; 70(12): 1579-1591.
12. William JI et al. Non-clinical pharmacology, pharmacokinetics, and safety findings for the antihistamine bepotastine besilate. *Current Medical Research & Opinion* 2010; 26(10): 2329–2338.
13. Ohashi et al. Effect of P Glycoprotein on intestinal absorption and brain penetration of Antiallergic agent Bepotastine Besilate. *Drugs Metabolism and Deposition* 2006; 34(5): 793-799.
14. Baba S, Takasaka T, Baba K, et al. Clinical trial of TAU-284 (betotastine besilate) on perennial allergic rhinitis: a double blind study in comparison with terfenadine [in Japanese] *Rinsho Iyaku* 1997; 13(5): 1307-35.
15. Baba S, Takasaka T, Baba K, et al. Long-term treatment of TAU-284 (betotastine besilate) on perennial allergic rhinitis [in Japanese]. *Rinsho Iyaku* 1997; 13(5): 1361-82
16. Baba S. Post-marketing surveillance study of Talion_ tablets on pediatric allergic rhinitis [in Japanese]. *Rinsho Iyaku* 2002; 18(12): 1371-87.
17. Baba K. Results from post-marketing surveillance studies of Talion_ tablets (bepotastine besilate) in patients with allergic rhinitis [in Japanese]. *J New Rem Clin* 2007 Feb 10; 56(2 Suppl.): 10-33.
18. Okubo K et al. Double-blind placebo-controlled study of bepotastine besilate in pediatric patients with perennial allergic rhinitis. *Expert Opin Pharmacother.* 2015;16(16): 2395-408.
19. Kanzaki S et al. Histamine antagonist Bepotastine suppresses nasal symptoms caused by Japanese cedar and cypress pollen exposure. *J Drug Assess.* 2016; 5(1): 15–23.
20. Takahashi H et al. Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal-and flare-response, sedation, and psychomotor performance. *Clin Exp Dermatol.* 2004 Sep; 29(5): 526-32.