

Research Article

Effectiveness of levocetirizine in treating allergic rhinitis while retaining work efficiency

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Abstract

The manifestation and severity of Allergic rhinitis symptoms show diurnal variation which negatively impacts the patient's quality of life, day-to-day activities, and productivity at the workplace. The symptoms worsen at night or early morning and therefore administration of levocetirizine towards evening may be more acceptable. Consequently, the present study evaluated the effectiveness of evening Levocetirizine administration on 24-hour symptom control, Physical and mental health, and daytime somnolence in patients with allergic rhinitis the study was a prospective, open-labeled, single-arm, two-center, observational study among patients with allergic rhinitis. Levocetirizine was prescribed as 5 mg or 10 mg once a day evening oral dose for at least 7 days before sleep. The 24-hour total nasal symptom scores (TNSS) for self-reported signs and symptoms of allergic rhinitis were recorded. Additionally, study evaluations included the SF-12 scale (Quality of Life), Stanford Sleepiness Scale (degree of sleepiness), and work productivity and activity impairment (WPAI) questionnaires. These evaluations were performed at baseline (Day 0) and at scheduled intervals of Day 1 (24-hour), Day 3, and Day 7. Results demonstrated that evening administration of Levocetirizine facilitates 24-hour symptom control while having no significant effect on daytime somnolence, daily activities, and the work productivity of patients.

Introduction

Allergic rhinitis is a chronic respiratory disease characterized by IgE-mediated inflammation of nasal mucosa. Rhinorrhea, sneezing, nasal blockage, and itching are some of the main signs and symptoms of allergic rhinitis [1,2]. In the medical treatment of allergic rhinitis, antihistamines are the primary focus of pharmacotherapy. Antihistamines alleviate these symptoms in both seasonal and perennial rhinitis types [3,4]. Second-generation antihistamines like cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine are the mainstay in suppressive therapy [5,6].

These antihistamines are essentially free of undesired central nervous system effects like somnolence when used at recommended levels. These drugs are far less likely to result in other unfavorable anticholinergic side effects typical of first-

generation antihistamines [3]. Therefore, second-generation antihistamines are recommended as the first-line treatment for allergic rhinitis, according to current management guidelines. Different second-generation antihistamines have a variable pharmacological profile, which may affect how well they suppress the proinflammatory mediators linked to an allergic manifestation [7].

Levocetirizine, the R-enantiomer of the racemate cetirizine is a selective H-1 antagonist. It has been shown to have a better efficacy profile than other second-generation antihistamines like desloratadine and fexofenadine for use in chronic rhinitis [8]. Improved safety profile may be attributed to the minimum crossing of the blood-brain barrier besides low cerebral receptor binding and modest volume of distribution. The lack of cardiotoxicity and mild nature of adverse effects do not compromise the patient's well-being in long-term therapy [9,10].

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Submitted: April 12, 2023

Approved: April 24, 2023

Published: April 25, 2023

How to cite this article: Yogesh D, Tanush S, Roheet R, Akhila P, Chaitanya VK, et al. Effectiveness of levocetirizine in treating allergic rhinitis while retaining work efficiency. Arch Asthma Allergy Immunol. 2023; 7: 005-011.

DOI: 10.29328/journal.aaai.1001031

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Keywords: Levocetirizine; Allergic rhinitis; Antihistaminics; Quality of life; Chrono-pharmacology

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Levocetirizine is recommended for the treatment of seasonal allergic rhinitis in adults and children above 2 years of age. According to a systematic review when compared to first-generation antihistamines, levocetirizine produced a lesser degree of sedative effects. Modest sedative effects with a risk ratio of 1.67 when compared with placebo were observed [11]. Allergic rhinitis patients often complain of somnolence if taking levocetirizine during day time which is a factor for non-adherence. By scheduling the administration of levocetirizine in the evening time, such side effects can be minimized. The half-life of Levocetirizine is around 24 hours. Therefore, a single administration of levocetirizine in the evening will be more acceptable. Studies evaluating change in the timing of levocetirizine intervention in the Indian population are lacking. Consequently, the current study sought to evaluate the effectiveness of Levocetirizine administered in the evening time on 24-hour symptom control and daytime somnolence in allergic rhinitis.

The application of chronopharmacology to the pathophysiology of allergic rhinitis is still under research and the present study is an effort in the same direction [12]. The allergic rhinitis symptoms and manifestation exhibit a chronobiological variation throughout the day. Most patients are symptomatic at night or early morning, which frequently interferes with sleep, negatively impacting their quality of life, daily activities, and academic and occupational performance. Therefore, the present study was designed with the hypothesis altering the timing of levocetirizine administration might help in better symptom control, and improve work performance, overall quality of life and drug adherence.

Materials and Methods

Study design

The study was a prospective, open-labeled, single-arm, two-center, observational study among patients with allergic rhinitis conducted at the Department of Otolaryngology and Dermatology, Dr. D Y Patil Medical College and Hospital, Navi Mumbai, Maharashtra, India.

This study was conducted in compliance with Ethics Committee (EC) requirements as per applicable regulations and also in compliance with ICH-GCP E6 (R2). All study documents were reviewed and approved by Institutional Ethics Committees (IEC) prior to the initiation of the study at the site.

Study participants

Fifty-five patients with allergic rhinitis were enrolled in the study. The sample size was calculated using a two-sided significance level of 95%, power of 99%, effect size of 0.5 and non-centrality parameter δ value of 4.281.

Test product, dose and mode of administration: Oral Levocetirizine, 5 mg or 10 mg OD evening dose was

administered to patients of allergic Rhinitis for at least 7 days before sleep.

Patients with allergic rhinitis

Male or female patients above 18 years of age with moderate-severe persistent or intermittent allergic rhinitis, advised Levocetirizine once daily evening treatment in routine clinical practice by treating physician were included in the study. Eligible patients had total nasal symptom scores greater than or equal to 6 points with congestion or with one or more symptoms (itching, runny nose, and sneezing) score greater than or equal to 2 at the screening visit.

Patients were excluded from the study if they had any abnormal clinical or laboratory findings, history of alcohol abuse or illicit drug use, pregnancy or risk of pregnancy and lactating patients, known hypersensitivity to the Levocetirizine components, receiving decongestants (nasal or oral) or allergen-specific immunotherapy or topical corticosteroids. Written informed consent was obtained from all study participants.

Study evaluations and follow-up time points

Patients were screened for eligibility on Day 0 prior to enrolment in the study. Self-administration of the prescribed dose was initiated by the enrolled patients on Day 0. The study evaluations were performed at baseline (Day 0) before treatment and at scheduled intervals of Day 1 (24-hour), Day 3, and Day 7. The follow-up was done either physically or telephonically. A 24-hour assessment was done for a reduction in the self-reported signs and symptoms of allergic rhinitis. Assessments were done on Day 1, Day 3, and Day 7 of enrolment, for absenteeism from work, reduced work performance, and the 12-point health-related quality of life.

Patients who completed the study for a period of 7 days/week were considered for the final assessment. Those patients who were taken off the drug or given any other medication due to recovery or other reasons were excluded from the study. A final assessment of vital signs was done on Day 7.

Efficacy endpoints

The following scales were used to assess efficacy variables during the study

Total Nasal Symptom Scores (TNSS): TNSS consists of three questions that assess nasal obstruction, itching/sneezing, and secretion/runny nose. The answer to each question is provided using a 4-point scale from 0 (no symptoms) up to 3 (severe symptoms) [13].

Physical and mental health: The SF-12 is a self-reported outcome measure that assesses the impact of physical and mental health on an individual's everyday life. It is often used as a quality-of-life measure. Scores range from 0 to 100, with higher scores indicating better physical and mental health functioning [14].

The Stanford Sleepiness Scale: The degree of sleepiness experienced by patients enrolled in this study was monitored using the Stanford sleepiness scale rating. A score above 3 is considered sleepy. Getting a better night's rest could improve the level of alertness and day-to-day performance of the patient [15].

Work productivity and activity impairment questionnaire: The Work Productivity and Activity Impairment (WPAI) questionnaire measures work time missed and work and activity impairment because of a specified health problem during the past 7 days [16].

Safety endpoints

At each assessment, all adverse events (AEs), whether previously known or not, were recorded with their description, intensity, action taken, duration, outcome, and opinion about the causal relationship to the study drugs.

Statistical analyses

Results were expressed as mean \pm SD for nominal data and as proportions for categorical data. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Wilcoxon Signed Rank Test for calculation of significance for TNSS allergic rhinitis symptoms, Stanford sleepiness scale, SF-12, and WPAI scores respectively post Levocetirizine treatment compared to baseline values.

Results

Disposition of patients

The cohort of patients with allergic rhinitis consisted of a total of 55 patients with an almost equal proportion of females (27 patients [49.09%]) and males (28 patients [50.91%]). There were no dropouts reported during the study and the data for all 55 patients with allergic rhinitis were used for analysis.

Demographic and other baseline characteristics

The frequency distribution based on demographic characteristics of patients with allergic rhinitis enrolled in the study is summarized in Table 1. Within the allergic rhinitis cohort, a greater frequency of patients was between 21-30 years of age (19 patients [34.55%]), had their height between 160 cm - 180 cm (31 patients [56.36%]), had their weight between 50-60 kg (33 patients [60.0%]), and had a BMI between 18.5-24.9 kg/m² (53 patients [96.36%]).

All patients with allergic rhinitis (55 patients [100.0%]) enrolled in this study, had normal systemic examination findings. None of the participants reported hypertension, diabetes, chronic obstructive pulmonary disorder (COPD), or asthma as comorbidities.

Efficacy results among patients with allergic rhinitis

Total Nasal Symptom Scores (TNSS): A statistically

significant reduction in nasal obstruction (p - value = 0.0000001013), itching/sneezing (p - value = 0.0000000020), and Secretion/runny nose mean scores (p - value = 0.0002075016) was observed on Day 1 (24-hour), Day 3 and Day 7 following treatment with Levocetirizine (Table 2, Figure 1).

Physical and mental health functioning

The mean SF-12 scores indication of 26.80 (± 2.63), before treatment with Levocetirizine, suggests a reduced physical and mental health functioning as an indicator of the quality of life in patients with allergic rhinitis. Following treatment with Levocetirizine, a non-significant (p - value = 0.1491758617) change in SF-12 scores from 26.80 (± 2.63) to 25.55 (± 1.82) was observed among patients with allergic rhinitis. Thus, Levocetirizine did not impair the physical and mental health functioning of allergic rhinitis. Patients (Figure 2).

Table 1: Frequency Distribution According to Demographic Characteristics.

S. No	Parameters	No of Patients	Percentage
1	Age Group (years)		
	18-20	5	9.09
	21-30	19	34.55
	31-40	15	27.27
	41-50	10	18.18
	51-60	4	7.27
	61-70	1	1.82
2	Height (cm)		
	140-160	23	41.82%
	160-180	31	56.36%
	> 180	1	1.82%
3	Weight (kg)		
	40-50	9	16.36
	50-60	33	60.0
	60-70	10	18.18
	70-80	2	3.64
4	BMI (kg/m ²)		
	< 18.5	0	0.00
	18.5-24.9	53	96.36
	> 25	2	3.64

BMI: Body Mass Index

Table 2: Time course of changes in mean scores for nasal symptoms following Levocetirizine administration.

S. No	Symptoms	Mean (\pm SD)	Percentage change	p value
1	Nasal Obstruction			0.0000001013
	Before treatment	2.64 (± 0.49)	2.07	
	Day 1	2.58 (± 0.50)	2.07	
	Day 3	2.35 (± 0.52)	11.03	
2	Itching/Sneezing			0.0000000020
	Before treatment	2.59 (± 0.50)	-	
	Day 1	2.58 (± 0.50)	0.42	
	Day 3	2.25 (± 0.58)	13.04	
3	Secretion/Runny nose			0.0002075016
	Before treatment	2.24 (± 0.54)	-	
	Day 1	2.24 (± 0.58)	0.00	
	Day 3	2.07 (± 0.57)	7.32	
	Day 7	1.93 (± 0.60)	13.82	

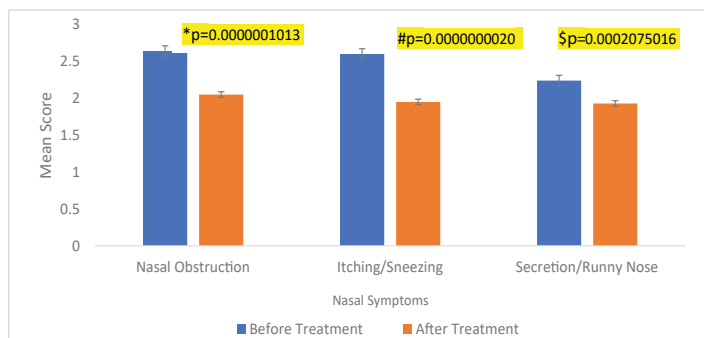


Figure 1: Effect of Levocetirizine on Symptoms for Allergic Rhinitis. BT: Before Treatment; AT: After Treatment; * $p < 0.05$ vs. Nasal obstruction BT score, # $p < 0.05$ vs. Itching/Sneezing BT score; § $p < 0.05$ vs. Secretion/Running Nose BT score

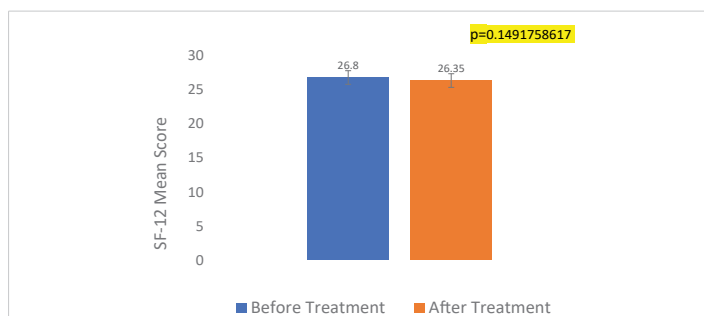


Figure 2: Effect of Levocetirizine on Quality of Life in Patients with Allergic Rhinitis. $p=0.1491758617$

The stanford sleepiness scale

The change in mean scores of sleepiness at morning, afternoon, and night time points was found to be 5.11%, 2.29%, and 2.82% following treatment with Levocetirizine. No significant change in the corresponding p - values for the degree of sleepiness at a different time of the day was observed (p - value = 0.226 [morning], 0.134 [afternoon], and 0.146 [night]) (Figure 3).

Work productivity and activity impairment questionnaire (WPAI)

The mean WPAI score following treatment with Levocetirizine showed a percent change of 12.36% (reduced from 53.68 to 47.05) after treatment. The corresponding p - value for the WPAI score was found to be statistically significant (p - value = 0.009) (Figure 4).

Safety results among patients with allergic rhinitis

Adverse events (AEs): None of the patients enrolled within the allergic rhinitis cohort reported any post-treatment adverse drug reactions/adverse events. There were no deaths, serious adverse events, or other significant adverse events reported during the study.

Vital signs, physical findings, and other observations related to safety

Changes in vital sign parameters (systolic blood pressure [p - value = 0.383], diastolic blood pressure [p - value = 0.920], pulse rate [p - value = 0.094], respiratory rate [p - value =

0.588], and body temperature [p - value = 0.442]) were not statistically significant. Follow-up changes observed in mean values for vital sign parameters in patients with allergic rhinitis are presented in Table 3.

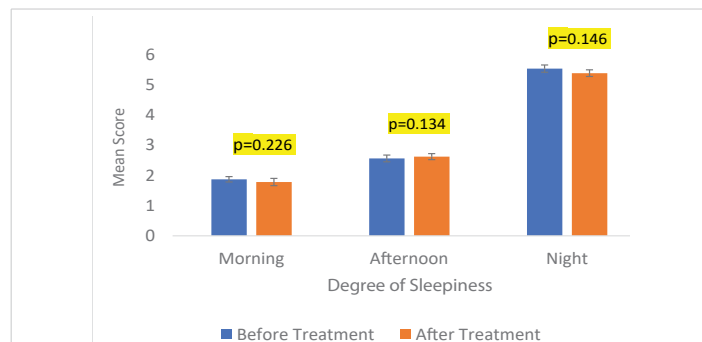


Figure 3: Effect of Levocetirizine on Degree of Sleepiness in Patients with Allergic Rhinitis.

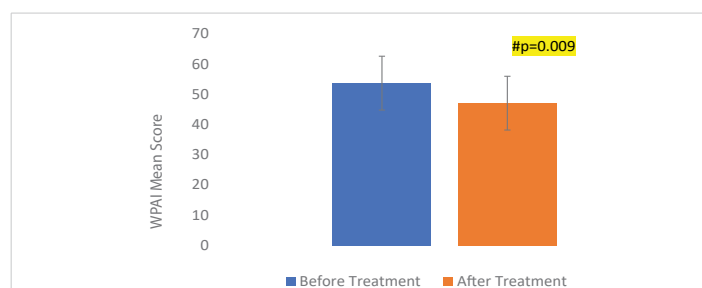


Figure 4: Effect of Levocetirizine on Work Productivity and Activity Impairment in Patients with Allergic Rhinitis. WPAI: Work Productivity and Activity Impairment. # $p < 0.05$ vs. Before Treatment score. # $p=0.009$

Table 3: Vital Signs, Physical Findings among allergic rhinitis patients following Levocetirizine Administration.

	Parameters	Mean	Standard Deviation	Percent Change	p value
1	Systolic Blood Pressure (mm Hg)				0.383
	Before treatment	120.00	3.71	-	
	Day 1	120.05	3.55	0.05	
	Day 3	119.53	3.29	0.39	
2	Diastolic Blood Pressure (mm Hg)				0.920
	Before treatment	76.33	5.43	-	
	Day 1	78.07	4.79	2.29	
	Day 3	78.53	7.29	2.88	
3	Pulse Rate (beats per minute)				0.094
	Before treatment	79.67	6.26	-	
	Day 1	80.05	8.42	0.48	
	Day 3	78.51	7.84	1.46	
4	Respiratory Rate (breaths per minute)				0.588
	Before treatment	16.96	2.38	-	
	Day 1	16.29	1.90	3.97	
	Day 3	16.56	2.03	2.36	
5	Body Temperature (°F)				0.442
	Before treatment	97.95	0.48	-	
	Day 1	97.75	0.47	0.20	
	Day 3	97.76	0.45	0.19	
	Day 7	97.76	0.41	0.19	



Discussion

Studies have shown that Allergic rhinitis negatively impacts patients' day-to-day activities and productivity at the workplace [17,18]. Quick symptom control can reduce the number of days lost at work resulting in an improvement in overall quality of life. Antihistamines with decongestant properties are in use for allergic rhinitis of varied severity for a long. Second-generation antihistamines cause minimum sedation, which was common with older-generation antihistamines. Therefore, second-generation antihistamines were preferred [19].

There are certain studies that have assessed the effectiveness of levocetirizine, in allergic rhinitis. Persistent Rhinitis Trial (Xyzal) was the first large, long-term clinical trial conducted among 551 patients with persistent rhinitis. Over the course of the 6-month treatment period, levocetirizine treatment was shown to improve quality of life, alleviate symptoms, and cut down on overall illness expenditures. Levocetirizine's effectiveness was assessed in the XYZAL trial utilizing a variety of clinical, Health-Related Quality of Life (HRQoL), and pharmacoeconomic measures carried out over an extended period of time using electronic diary cards [20].

Subsequently, the XPERT study, which involved 551 participants, was a 6-month, double-blind, placebo-controlled, multicenter, international trial. Adults with chronic rhinitis who were allergic to house dust mites and grass pollen were randomised to receive levocetirizine 5 mg/d or a placebo. After six months of treatment, levocetirizine improved the symptoms and quality of life associated with allergic rhinitis while also lowering the overall costs of treatment [21].

Chronobiology and chronotherapy of allergic rhinitis

However, there is a paucity of studies exploring the application of chronopharmacology in allergic rhinitis since the manifestation and severity of Allergic rhinitis symptoms show diurnal variation [12]. The symptoms worsen at night or early morning resulting in poor daytime quality of life, impaired work performance, irritability, and poor attention [22,23]. Therefore, the evening administration of levocetirizine, has been studied in the present investigation. It was hypothesized that by altering the timing of Levocetirizine drug administration, a further improvement in 24-hour allergic rhinitis symptom control may be observed. This will also translate to reduced daytime somnolence, alteration in work performance, daily activities, and workdays lost due to allergic rhinitis.

Efficacy of levocetirizine

In patients with allergic rhinitis, effective 24-hour symptom control following evening administration of oral Levocetirizine was observed. Significant reductions in the mean scores of symptoms such as nasal obstruction, itching/sneezing, and secretion/runny nose were noted. There are

similar studies that have demonstrated the effectiveness of levocetirizine in attenuating nasal symptoms. A study conducted by Jorissen, et al. 2006 showed that levocetirizine improved symptom control for allergic rhinitis and was well tolerated. A statistically significant decrease compared to baseline was observed for each individual symptom of the global T4SS scale (combined score of sneezing, rhinorrhoea, nasal and ocular pruritus) [24]. However, in the present study, the timing of levocetirizine administration was altered to night time dose.

Recently, a study conducted by Vanitha, et al. 2021 reported that the newer antihistaminic Bilastine is equally efficacious as levocetirizine in the treatment of allergic rhinitis. Though there is clinical significance in the treatment of allergic rhinitis between the groups, there is no statistical significance that would prove Bilastine is clinically superior to Levocetirizine for allergic rhinitis treatment [25].

SF-12 is a validated scale used to assess physical and mental health functioning and [14]. In the present study, the low mean SF-12 scores indicated a reduced quality of life in patients with allergic rhinitis. Levocetirizine did not impair the physical and mental health functioning of allergic rhinitis. Following treatment with Levocetirizine, a non-significant change in the mean SF-12 score was observed as compared to the pre-treatment score. Although levocetirizine administration improved the clinical symptoms of allergic rhinitis, it did not translate into a significant improvement in physical and mental health functioning. These results are in contradiction to the observations by Segall, et al, 2010 who reported improvement in quality of life with levocetirizine in US patients with seasonal allergic rhinitis [26]. However, the authors used a disease-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) compared to SF-12 used in the present study. The patients with allergic rhinitis did not report a significant change in the degree of sleepiness in the morning, afternoon, and evening time points after treatment with Levocetirizine emphasizing that the drug does not produce significant somnolence. Similar results were reported by Tzanetos, et al. 2011. It was reported that most patients with a perceived history of sedation with cetirizine were able to tolerate levocetirizine [27].

Allergic rhinitis significantly impacted the work productivity and activity of patients and workdays lost were found to be significant. Nonetheless, post levocetirizine administration, a significant improvement in the mean WPAI score, an indicator of Work Productivity and Activity Impairment was observed. Results concur with the findings of a study conducted by Segall, et al. 2010 [26] Levocetirizine was well tolerated and was found to be significantly more effective than placebo in improving the naso-ocular symptoms and health-related quality of life in patients with Seasonal allergic rhinitis. The Quality of Life, Work Productivity, and Activity were assessed at week 1, week 2, and the end of treatment.



Recently a study conducted by Sushitra, et al. 2020 compared the safety, effectiveness, and cost-effectiveness of the Combination of Levocetirizine and Fexofenadine with Montelukast in Allergic Rhinitis and its effect on Quality of Life. Both Levocetirizine and Fexofenadine in combination with Montelukast showed significant improvement as compared to baseline in terms of total nasal symptom scores and total ophthalmic symptom scores. Patients in the Levocetirizine group had a comparatively better quality of life, lesser side effects, and low cost of therapy [28].

Safety of levocetirizine

None of the patients with allergic rhinitis experienced any new or unexpected findings safety findings. The changes in systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature were not significant following treatment with Levocetirizine.

Conclusion

The effectiveness of evening Levocetirizine administration on 24-hour symptom control, Physical and mental health, and daytime somnolence in patients with allergic rhinitis was evaluated in the present study. Levocetirizine was prescribed as 5 mg or 10 mg once a day evening oral dose for at least 7 days before sleep. The 24-hour total nasal symptom scores (TNSS) for self-reported signs and symptoms of allergic rhinitis, SF-12 scale (physical and mental functioning), Stanford Sleepiness Scale (degree of sleepiness) and work productivity and activity impairment (WPAI) questionnaires were evaluated.

Safety conclusion

Levocetirizine administration did not alter the systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature as compared to baseline values. No treatment-emergent adverse events were reported.

Efficacy conclusion

To conclude, results demonstrated that evening administration of Levocetirizine provides 24-hour symptom control, and does not impair the daily activities, or work productivity of patients while minimizing somnolence during morning, afternoon, and night time. Applying the principles of chronobiology for the prescription of Levocetirizine in the evening time is an effective and safe option for the management of allergic rhinitis. However, the newer third generation of antihistamines is in the pipeline as a promising alternative.

Acknowledgment

We wish to thank all the patients, family members, and staff from all the units that participated in the study. We acknowledge Renovare Healthcare Solutions, India for their

medical writing and editing support, which was sponsored by Reddy's Laboratories Pvt Ltd., India.

Funding information

The study was funded by Dr. Reddy's Laboratories Pvt Ltd., India.

References

1. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med.* 2015 Jan 29;372(5):456-63. doi: 10.1056/NEJMcp1412282. PMID: 25629743; PMCID: PMC4324099.
2. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001 Jul;108(1 Suppl):S2-8. doi: 10.1067/mai.2001.115569. PMID: 11449200.
3. Tran NP, Vickery J, Blaiss MS. Management of rhinitis: allergic and non-allergic. *Allergy Asthma Immunol Res.* 2011 Jul;3(3):148-56. doi: 10.4168/aair.2011.3.3.148. Epub 2011 May 20. PMID: 21738880; PMCID: PMC3121056.
4. Kawauchi H, Yanai K, Wang DY, Itahashi K, Okubo K. Antihistamines for Allergic Rhinitis Treatment from the Viewpoint of Nonsedative Properties. *Int J Mol Sci.* 2019 Jan 8;20(1):213. doi: 10.3390/ijms20010213. PMID: 30626077; PMCID: PMC6337346.
5. Canonica GW, Blaiss M. Antihistaminic, anti-inflammatory, and antiallergic properties of the nonsedating second-generation antihistamine desloratadine: a review of the evidence. *World Allergy Organ J.* 2011 Feb;4(2):47-53. doi: 10.1097/WOX.0b013e3182093e19. Epub 2011 Feb 23. PMID: 23268457; PMCID: PMC3500039.
6. Rao S, Pai S, Vaidya KA, Shanbhag TV. Efficacy, safety and cost effectiveness of Levocetirizine and ebastine in allergic rhinitis: a comparative study. *International Journal of Basic & Clinical Pharmacology.* 2018; 7(9): 1748–1751.
7. Church MK, Church DS. Pharmacology of antihistamines. *Indian J Dermatol.* 2013 May;58(3):219-24. doi: 10.4103/0019-5154.110832. PMID: 23723474; PMCID: PMC3667286.
8. Godse K, Jain A, Pharande P. Comparative Efficacy Of Fexofenadine And Levocetirizine In Chronic Idiopathic Urticaria *Indian J Dermatol.* 2007;52(4):212.
9. Walsh GM. The anti-inflammatory effects of levocetirizine--are they clinically relevant or just an interesting additional effect? *Allergy Asthma Clin Immunol.* 2009 Dec 17;5(1):14. doi: 10.1186/1710-1492-5-14. PMID: 20066054; PMCID: PMC2804563.
10. Netti E, Calogiuri GF, Di Leo E, Cardinale F, Macchia L, Ferrannini A, Vacca A. Once daily levocetirizine for the treatment of allergic rhinitis and chronic idiopathic urticaria. *J Asthma Allergy.* 2008 Dec 16;2:17-23. doi: 10.2147/jaa.s3022. PMID: 21437140; PMCID: PMC3048603.
11. Snidvongs K, Seresirikachorn K, Khattiyawittayakun L, Chitsuthipakorn W. Sedative Effects of Levocetirizine: A Systematic Review and Meta-Analysis of Randomized Controlled Studies. *Drugs.* 2017 Feb;77(2):175-186. doi: 10.1007/s40265-016-0682-0. PMID: 28070872.
12. Smolensky MH, Lemmer B, Reinberg AE. Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. *Adv Drug Deliv Rev.* 2007 Aug 31;59(9-10):852-82. doi: 10.1016/j.addr.2007.08.016. Epub 2007 Aug 17. PMID: 17900748.
13. Singh-Franco D, Ghin HL, Robles GI, Borja-Hart N, Perez A. Levocetirizine for The Treatment Of Allergic Rhinitis And Chronic Idiopathic Urticaria In Adults And Children. *Clin Ther.* 2009;31(8):1664-1687.
14. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996 Mar;34(3):220-33. doi: 10.1097/00005650-199603000-00003. PMID: 8628042.



15. Hoddes E, Dement W, Zarcone V. The Development and Use of The Stanford Sleepiness Scale (SSS). *Psychophysiology*. 1972; 9: 150.
16. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993 Nov;4(5):353-65. doi: 10.2165/00019053-199304050-00006. PMID: 10146874.
17. de la Hoz Caballer B, Rodríguez M, Fraj J, Cerecedo I, Antolín-Amérigo D, Colás C. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the Cross-sectional study to evaluate work Productivity in allergic Rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy*. 2012 Sep-Oct;26(5):390-4. doi: 10.2500/ajra.2012.26.3799. PMID: 23168153; PMCID: PMC3904041.
18. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001 Jul;108(1 Suppl):S2-8. doi: 10.1067/mai.2001.115569. PMID: 11449200.
19. Wang XY, Lim-Jurado M, Prepageran N, Tantilipikorn P, Wang de Y. Treatment of allergic rhinitis and urticaria: a review of the newest antihistamine drug bilastine. *Ther Clin Risk Manag*. 2016 Apr 13;12:585-97. doi: 10.2147/TCRM.S105189. PMID: 27110120; PMCID: PMC4835134.
20. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, Van Cauwenberge PB, Van Hammée G; XPERT Study Group. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol*. 2004 Oct;114(4):838-44. doi: 10.1016/j.jaci.2004.05.070. PMID: 15480324.
21. Rogkakou A, Villa E and Garelli V, Canonica GW. Persistent Allergic Rhinitis and the XPERT Study. *WAO Journal* • March 2011, Supplement Allergic Rhinitis and The XPERT Study. *Ann Allergy Asthma Immunol*. B-ENT. 2006;2(2):55-62.
22. Stuck BA, Czajowski J, Hagner AE, Klimek L, Verse T, Hörmann K, Maurer JT. Changes in Daytime Sleepiness, Quality Of Life, And Objective Sleep Patterns In Seasonal Allergic Rhinitis: A Controlled Clinical Trial. *J Allergy Clin Immunol*. 2004;113:663–8.
23. Crystal-Peters J, Crown WH, Goetzel RZ, Schutt DC. The cost of productivity losses associated with allergic rhinitis. *Am J Manag Care*. 2000 Mar;6(3):373-8. PMID: 10977437.
24. Jorissen M, Bertrand B, Stiels B, Vandenbulcke K. Levocetirizine as treatment for symptoms of seasonal allergic rhinitis. *B-ENT*. 2006;2(2):55-62. PMID: 16910288.
25. Vanitha M, Sowmini K, Kumari SS, Reddy RN. Efficacy of Oral Bilastine in Comparison with Levocetirizine in Allergic Rhinitis A Randomised Clinical study. *Journal of Clinical and Diagnostic Research*. 2021;15(8): FC01-FC0
26. Segall N, Gawchik S, Georges G, Haeusler JM. Efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in US adults with seasonal allergic rhinitis: a randomized, placebo-controlled study. *Ann Allergy Asthma Immunol*. 2010 Mar;104(3):259-67. doi: 10.1016/j.anai.2009.12.003. PMID: 20377116.
27. Tzanetos DB, Fahrenholz JM, Scott T, Buchholz K. Comparison of the sedating effects of levocetirizine and cetirizine: a randomized, double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2011 Dec;107(6):517-22. doi: 10.1016/j.anai.2011.08.012. Epub 2011 Sep 19. PMID: 22123381.
28. Suchita, Sharma DK, Kaur G, Singh A, Bhagat S, Matreja PS. Comparison of safety, effectiveness and cost effectiveness of Combination of Levocetirizine and Fexofenadine with Montelukast in Allergic Rhinitis and its effect on Quality of Life. *International Archives of BioMedical and Clinical Research*. 2020; 6(2): 5-8.