Original Article

Comparision Of Efficacy Of Levocetirizine With Montelucast And Levocetirizine Alone In Persistent Allergic Rhinitis

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Objective: To compare the efficacy of levocetirizine with montelukast and levocetirizine alone in patients with persistent allergic rhinitis in our setup.

Material and Methods: Patients with symptoms of AR attending ENT clinic were registered and divided into two groups based on drug given. Patients with odd numbers were included in group A receiving levocetirizine 5mg with montelukast 10mg once daily while patients with even numbers were included in group B receiving only levocetirizine 5mg once daily. Data was collected at visit 1 prior to medication, visit 2 one week after medication and visit 3 two weeks after medication. Medication history review, nasal symptom assessment and anterior rhinoscopy were done at each visit. Patients were evaluated for rhinorrhea, sneezing, nasal itching and nasal obstruction on a scale. Total symptom complex score (TSCS) was calculated by adding scores of all four variables under study using proforma. Lower the score more effective will be the drug.

Results: 124 patients were included in study; 63 male and 61 female. TSCS was 9 -10 in 73.3% patients at visit 1 in levocetirizine group that improved to 4 5 in 28.3% and 3 - 4 in 65% patients at visit 2 and 3 respectively. Patients receiving levocetirizine had TSCS of 9 to 10 in 52.9% at visit 1 with an improvement to 3 - 4 in 9.4% and 49.1% at visit 2 and visit 3 respectively. **Conclusion:** Levocetirizine with montelukast is superior to levocetirizine alone in controlling overall symptoms of AR in our study.

Key words: Allergic rhinitis, Montelucast, Leukotriene receptor antagonist , Levocetirizine

Introduction

Persistent allergic rhinitis (PAR) is a chronic inflammatory condition characterized by variety of nasal signs and symptoms not only impairing physical and social functioning but also increasing financial burden[1]. Antihistamines are mainstay of treatment[2]. Third generation antihistamines (levocetirizine and desloratadine) are amongst newer drugs that are gaining popularity due to their non-sedative, prolonged, safe and well-tolerated effects. Levocetirizine, a highly selective H_1 antihistamine, has additional benefits of nasal decongestion improving nasal airflow and is cost effective.[3, 4, 5, 6] It has both short term and long term beneficial effects in the management of allergic rhinitis.[7] Monotherapy with antihistamines is no more a best option. Combination therapy is considered as superior because of the fact that an allergic person is hypersensitive to multiple allergens. Addition of montelucast, a leukotriene receptor antagonist (LRA), to an antihistamine has a demonstrated effectiveness in treating PAR [8, 9]. It has proven efficacy in terms of improving nasal symptoms and quality of life [10]. It has no significant drug interactions with additional benefits of having high safety profile and tolerability even after prolonged use.[11]

Purported significance of this study is to select a better remedy in terms of alleviating symptoms of allergic rhinitis using drugs that will be more effective with minimum untoward effects.

Patients and Methods

Patients were collected from outdoor department of ENT Pakistan Institute of Medical Sciences Islamabad from 18th October 2008 to 17th April 2009. 124 patients with symptoms of AR attending ENT clinic were registered and divided into two groups based on drug given. Patients were included based on demographic data, medical history, drug history and history of nasal allergy. Patients with odd numbers were included in group A receiving levocetirizine 5mg and montelukast 10mg once daily while patients with even numbers were included in group B receiving only levocetirizine 5mg once daily. All patients were allocated into two groups by non - probability (convenience) sampling. Patients with bronchial asthma, nasal polyps and pregnant and lactating mothers were excluded from study. Informed consent was obtained prior to initiation of drug therapy as a part of ethical concern about

inclusion in study, medicine given and benefits and risks involved. Data was collected at visit 1 prior to medication, visit 2 one week after medication and visit 3 two weeks after medication. Medication history review, nasal symptom assessment and anterior rhinoscopy were done at each visit. Patients were evaluated for rhinorrhea, sneezing, nasal itching and nasal obstruction on a scale. Total symptom complex score (TSCS) was calculated by adding scores of all four variables under study using proforma. The efficacy of levocetirizine with montelukast was defined by their ability to reduce patient's symptoms of rhinorrhea, sneezing, nasal itching and/or nasal obstruction after two weeks of treatment. This was judged as per following scale:

1. No rhinorrhea	1. No sneezing
2. Mild rhinorrhea	2. Mild sneezing
3. Moderate rhinorrhea	3. Moderate sneezing
4. Severe rhinorrhea	4. Severe sneezing
1. Nasal obstruction absent	1. Nasal itching absent
2. Nasal obstruction present	2. Nasal itching present

Efficacy was determined not only on the basis of individual variable score but also on total symptom complex score (sum of all four variable). Lower the score, more effective would be the drug. The patients who did not have impairment of sleep, daily activities or work in school or no troublesome symptoms were labeled as having mild disease. The patients who had one or more of these symptoms without leave from work were considered as having moderate disease while those with leave from work were having severe disease. The data was stored and analyzed in SPSS (10). Descriptive statistics were used to calculate mean and standard deviation for age. Frequency (percentages) was calculated for values of gender, rhinorrhea, sneezing, nasal itching and nasal obstruction. Chi-square test and independent samples t test were used as test of significance. P value of <0.05 was considered as significant.

Results

A total of hundred and twenty four patients were included in this study over a period of six months from Oct 2008 to April 2009. The patients were divided into two groups; group A (patients with odd numbers) and group B (patients with even numbers). Group A was given levocetirizine 5mg with montelukast 10mg once daily and group B was given levocetirizine 5mg alone for 2 weeks. The age of patients varied from 13 to 46 years with a mean age of 22 years. Standard Deviation for age was 7.5012. The two groups did not differ statistically with respect to age distribution (p=.157). Gender distribution was in favor of males with 63 males and 61 females. Chi-square test was used to determine the efficacy of drugs on individual variables that revealed statistically no significant difference between the two drug groups for rhinorrhea p=1.00 and nasal itching p=.341. However the other two individual variables showed significant difference in improvement between two

Table-1: CHI-square test for individual variable scores at all visits p-values.

Symptom	Severity	Group A			Group B			P Value		
		Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Rhinorrhea	No	02	05	29	04	08	28	.665	.363	1.00
	Mild	05	20	19	05	24	21			
	Moderate	18	23	03	24	24	09			
	Severe	30	01		25					
Sneezing	No		02	10		03	19	.934	.000	.000
	Mild	01	13	23	03	21	28			
	Moderate	11	33	05	20	24	09			
	Severe	39	01	01	25	04				
Nasal obstruction	Present	57	09	03	49	15	02	.254	.000	.001
	Absent	05	33	49	13	47	60			
Nasal Itching	Present	49	09	06	52	04	03	.716	.001	.431
	Absent	11	33	56	10	58	59			

groups (Sneezing p=.000 and nasal obstruction p=.001). The details of individual variable score at each visit and p values is given in **table-I.** Independent samples t test was used to determine the overall efficacy of treatment regimen according to which mean initial Total Symptom Complex Score (TSCS) was 8.8 in group A and 8.2 in group B before the start of medications. At visit 2 It improved to 5.0 and 5.6 and at visit 3 it is further lowered to 3.8 and 4.6 respectively in both groups. The details at each visit with p values is given in **table-II.**

Table-2: Mean Total Symptom Complex Score (TSCS) at various visits.

Groups	A	B	Percentage
Mean TSCS at visit 1	8.8	8.2	.205
Mean TSCS at visit 3	5.5	5.6	.001
Mean TSCS at visit 3	3.8	4.6	.000

These results of independent samples t test showed that there is significant difference between the overall efficacy of levocetirizine and levocetirizine/ Montelukast (p=.000); levocetirizine/Montelukast being more effective than levocetirizine alone after two weeks of treatment.

Persistent mild symptoms of rhinorrhea were reported in 40 patients (35%) while persistent mild sneezing in 51 (47%) patients in total study population at the completion of treatment at visit 3 with statistically no significant difference. Nasal obstruction and nasal itching were well controlled in both groups with statistically no significant difference.

Discussion

Allergic rhinitis represents a global health problem. In recent times, the incidence of allergic diseases has been increasing worldwide[12]. Published data on the prevalence of allergic diseases is lacking in Pakistan[13]. In allergic rhinitis, treatment is directed towards the inflammatory response. Avoidance of allergens is counseled but medication is usually needed for better control. This entails the use of oral antihistamines with or without other modes of therapy. Antihistamines were introduced more than 50 years ago for the treatment of allergic rhinitis. Although first-generation antihistamines are clinically effective and are still available, their use is limited by their central nervous system (CNS) effects such as somnolence, sedation, drowsiness, fatigue, loss of attention and impaired psychomotor performance as well as anticholinergic effects including difficulty in micturition, impotence, constipation and other gastrointestinal symptoms[14]. Because of the sedative effects these drugs should be avoided in patients who undertake activities such as driving. They are not the drugs of choice in children and in geriatrics. The second-generation antihistamines have a more favorable side-effect profile lacking substantial sedative properties and have largely supplanted the earlier drugs[15].The results of present study offer insights on beneficial antihistaminic actions of levocetirizine alone and in combination with LRA. We found that levocetirizine with montelukast achieves superior control of allergic manifestations with better control for sneezing, nasal obstruction and itching(p=< .05) . As for as rhinorrhea is concerned no significant difference was noticed between two groups (p=.361, p=1). Schapowal et al investigated the efficacy of cetirizine in seasonal allergic rhinitis and observed the improvement in symptom severity scores[16]. A case-control study conducted by Walker in United Kingdom in teenagers found symptomatic allergic rhinitis and antihistamine use are associated with significantly increased risk of unexpectedly dropping a grade in summer examinations. This was attributed not only to disease impact on quality of life but also to impaired cognition by antiallergic medicines[17]. We in our study only assessed the beneficial antihistaminic effects without considering the side effects of both drugs. Walsh found levocetirizine an effective tool not only for immediate short-term allergic manifestations but also for long-term symptomatic relief [18]. This is consistent with our findings where combination therapy with levocetirizine showed greater reduction in TSCS in significantly more patients than that shown by levocetirizine alone at visit three (two weeks after the drug)(p=.000). Day and Briscoe assessed the efficacy of loratadine and montelukast upon nasal congestion and found that loratadine-montelukast treatment resulted in greater improvement in the mean nasal congestion score vs placebo.[19] Ciprandi and co in a pilot study reported decongestant effects about levocetirizine due to its better response to the symptom of nasal onstruction.[4] These results were similar to our inference where levocetirizine-montelukast treatment showed better response not only for nasal obstruction but also for sneezing and nasal itching (p=<.05). Characteristically no statistically significant difference was noted for runny nose. (p=.361 at visit 2 , p=1 at visit 3)

We found remarkably good overall control rate in

total cohort was 41.9% while mild symptoms were persisted in 39.5% patients. As for as individual symptom cure is concerned it was better for nasal itching (91%) followed by nasal obstruction (89.7%), rhinorrhea (65%) and sneezing (49%) for total study population. Combination therapy with addition of local and/or systemic decongestants, a local steroid or even a first-generation antihistamine at a different timing may even be considered a superior approach in persistent AR.[20] However, the efficacy and side effects of such regimens needs to be rigorously evaluated and next-day sedation has been observed with such a regimen especially when combination of two antihistamines from different classes is used.[21]

A controlled study by Bousquet, Lund and Cauwenberge found that therapy for AR directed by a set of simple guidelines is more effective than therapy chosen by physicians.[22] ARIA guidelines are now available that recommends stepwise approach to treat AR keeping in consideration the potentially troublesome links of the disease especially with bronchial asthma.[23] These guidelines clearly address the severity of symptoms and quality of life parameters but there is a lack of quantitative analysis for severity assessment. A visual analog scale (VAS) is therefore recommended to assess the severity of symptoms of AR[24]. We in our study did not use this scale. Instead symptoms were categorized into mild, moderate or severe based on the presence of impairment of sleep, daily activities or work in school or troublesome symptoms with or without holidays from daily activities. We encountered an overall better response of levocetirizine with montelukast as compared to levocetirizine alone after one and two weeks of therapy (p=.000). Similar results were produced by Horak, Ciprandi and Day.[4]

Conclusion

There is statistically significant difference between levocetirizine -montelukast and levocetirizine alone as for as the improvement in most of the individual symptoms in symptomatic allergic rhinitis is concerned. Overall efficacy of combination therapy with levocetirizine and montelukast is more than levocetirizine alone in improving total symptom complex score in our study.

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References

1. Nathan R.A. The burden of allergic rhinitis. Allergy Asthma Proc.2007;28:3-9
2. Rose P, Marie A. Diagnosis and management of allergic rhinitis in adults. Med Today. 2007;5:45-8.
3. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. Ann Allergy Asthma Immunol. 2004;92:294-303.
4. Ciprandi G, Cirillo I, Vizzaccaro A, Civardi E, Barberi S, Allen M, et al. Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with percenial allergic rhinitis: a pilot study, Int Immunopharmacol. 2005;5:1800-8.
5. Bousquet J, Demarteau N, Mullol J, Van Davmme, Van GE, Bachert C, et al. Costs associated with persistent allergic rhinitis are reduce by levocetirizine. Allergy. 2005;60:788-94.
6. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. J Allergy Clin Immunol. 2004; 114:838-44.
7. Holgate S, Powell R, Jenkins M, Ali O.A. treatment for allergic rhinitis: a view on the role of levocetirizine. Curr Med Res Opin. 2005; 21:1099-106.
8. Storms W. Update on montelukast and its role in the treatment of asthma, allergic rhinitis and exercise-induced bronchoconstriction. Expert Opin Pharmacother. 2007;8:2173-87.
9. Borderias L, Mincewicz G, Paggiaro PL, Guilera M, Sazonov Kocevar V, Taylor SD, et al. Asthma control in patients with asthma and allergic rhinitis receiving add-on montelukast therapy for 12 months: a retrospective observational study. Curr Med Res Opin. 2007; 28:296-304.
10. Philip G, Williams-Herman D, Patel P, Weinstein SF, Alon A, Gilles L, et al. Efficacy of montelukast for treating perennial allergic rhinitis. Allergy Asthma Proc. 2007;28:296-304.
11. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. Drugs. 2007;67:887-901.
12. Lehman JM, Blaiss MS. Selecting the optimal oral antihistamine for patients with allergic rhinitis. Drugs 2006;66:2309-19
13. Pfaar O, Raap U, Holz M,

Hörmann K, Klimek L. Pathophysiology of itching and sneezing in allergic rhinitis. Swiss Med Wkly 2009;139:35-40
14. Simons FE. Advances in H1-antihistamines. N Engl J Med 2004 ; 351:2203-17
15. Bender BG, Berning S, Dudden R, Milgrom H, Tran ZV. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. J Allergy Clin Immunol 2003;111:770-68
16. Schapowal A; Petasites Study Group. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis BMJ 2002; 324:144-146.
17. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. J. Allergy Clin. Immunol 2007; 120: 3817.
18. Walsh GM. A review of the role of levocetirizine as an effective therapy for allergic disease. Expert Opin Pharmacother 2008;9:859-67
19. Day JH, Briscoe MP, Ratz JD, Danzig M, Yao R. Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit. Ann Allergy Asthma Immunol. 2009;102:328-38
20. Dhanya NB, Thasleem Z, Rai R, Srinivas CR. Comparative efficacy of levocetirizine, desloratidine and fexofenadine by histamine wheal suppression test. Indian J Dermatol Venereol Leprol 2008;74:361-3
21. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. Am J Med 2004;116:338-344.
22. Bousquet J, Lund VJ, van Cauwenberge P. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy 2003;58:733-741.
23. Bachert C, Jorissen M, Bertrand B, Khaltaev N, Bousquet J. Allergic Rhinitis and its impact on asthma update (ARIA 2008). The Belgian perspective. B-ENT 2008;4:253-7
24. Casale TB, Blaiss MS, Gelfand E, et al. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. J Allergy Clin Immunol 2003;111:835-842