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Montelukast: a better alternative than antihistaminics in allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis is associated with sleep disturbances, daytime somnolence, and fatigue. Hence, present study was undertaken to evaluate and compare the nocturnal symptoms such difficulty in going to sleep, night time awakening and nasal congestion/obstruction on awakening among allergic rhinitis patients after administration of montelukast, chlorpheniramine meleate, levocetrizine, desloratidine and fexofenadine and to find out anti-allergic drug with maximum improvement in total symptom complex score.
Methods: The present study comprised of 125 patients suffering from allergic rhinitis on the basis of characteristic history, corroborative physical findings and blood eosinophilia. Night times symptoms including difficulty in going to sleep, night time awakenings and nasal congestion on awakening were evaluated after patients were given oral treatment with chlorpheniramine maleate, levocetrizine, fexofenadine, desloratadine and montelukast for a period of 6 weeks in different 5 groups and the result interpreted on the basis of symptoms relieved. Symptoms were recorded on day 1, 2 weeks, 4 weeks and 6 weeks of treatment and analysed. All the patients were randomly divided into five groups of 25 each. The results were tabulated and analyzed by chi-square, Kruskal-Wallis test.
Results: The present study found that levocetirizine provided immediate effect at 2 weeks which is significantly better than other drugs. But at 6 weeks, montelukast is best among the drugs which were compared; followed by levocetrizine, fexofenadine, and desloratadine and chlorpheniramine maleate. Montelukast was found to be a better drug as it has no significant side effects. Desloratadine group had dryness of mouth. Chlorpheniramine maleate has maximum side effects. 6 patients who took chlorpheniramine maleate complained of sedation, 1 patient complain of psychomotor disturbance.
Conclusions: The present study concludes that in terms of clinical efficacy, safety/tolerability and improvement in night time symptom scores at six weeks therapy in allergic rhinitis, montelukast is the better drug.

Keywords: Allergic rhinitis, Antihistamines, Montelukast, Levocetrizine, Desloratidine, Fexofenadine

INTRODUCTION

Allergic rhinitis is an immunoglobulin E–mediated disease, thought to occur after exposure to indoor and outdoor allergens such as dust mites, insects, animal danders, molds and pollens. Symptoms include rhinorrhea, nasal congestion, obstruction, and pruritus.[1] It is associated with sleep disturbances, daytime somnolence, and fatigue. The exact relationship between rhinitis and sleep disturbance is unknown; however, both

the symptoms and underlying pathology of allergic rhinitis can interfere with sleep quality. Nasal congestion, which has been shown to cause sleep-disordered breathing, is thought to be primarily responsible for rhinitis-related sleep disorders. The severity of nasal congestion follows a circadian rhythm, being worst at night and in the early morning.[2]

Chronotherapy is the study of the effects of the administration of medication in coordination with the body's circadian rhythms to maximise therapeutic effectiveness and minimise/avoid adverse effects.[3,4] Chronotherapy studies in allergic rhinitis suggest there are benefits to night-time dosing of antiallergy medications.[2] Hence, present study was undertaken to evaluate and compare the nocturnal symptoms such difficulty in going to sleep, night time awakening and nasal congestion/obstruction on awakening among allergic rhinitis patients after administration of montelukast, chlorpheniramine meleate, levocetrizine, desloratidine, fexofenadine and to find out anti-allergic drug with maximum improvement in total symptom complex score.

METHODS

The present study comprised of 125 patients attending the ENT outpatient department from period of May 2012 to April 2013 of Rajindra Hospital, Patiala. Patients were of varying age groups between 10-55 years, of either sex clinically been diagnosed as suffering from allergic rhinitis on the basis of characteristic history, corroborative physical findings and blood eosinophilia. Informed consent was taken from the patient fulfilling the above criteria after explaining them about the type of study being carried out. Night times symptoms including difficulty in going to sleep, night time awakenings and nasal congestion on awakening were evaluated after patients were given oral treatment with chlorpheniramine maleate, levocetrizine, fexofenadine, desloratadine and montelukast for a period of 6 weeks in different 5 groups and the result interpreted on the basis of symptoms relieved. Symptoms were recorded on day 1, 2 weeks, 4 weeks and 6 weeks of treatment and analysed. All the patients were randomly divided into five groups of 25 each.

Table 1: Total symptom score (TSS) Evaluation.

Night Time Symptoms	Night Time Symptom Score			
	0	1	2	3
	No	1-4	5-9	>10
Difficulty going to sleep	No	Mild	Moderate	Severe
Night time awakenings	No	Mild	Moderate	Severe
Nasal congestion on awakening	No	Mild	Moderate	Severe

*The subjective assessment for the degree of relief of symptoms were done according to total symptom score (TSS) from 0 to 3, 0=No symptom, 1=mild, 2=moderate, 3=severe, The results were tabulated and analysed by chi-square, Kruskal-Wallis test.

- Patients of Group 1 were given tablet montelukast 10 mg OD.
- Patients of Group 2 were given tablet Levocetrizine 5 mg OD.
- Patients of Group 3 were given tablet Fexofenadine 180 mg OD.
- Patients of Group 4 were given tablet Desloratadine 5 mg OD.
- Patients of Group 4 were given tablet Chlorpheniramine maleate 4 mg TDS.

Each patient was followed up after 2 week and then, after 4 and 6 weeks for the following parameters.

RESULTS

The Table 2 shows that symptoms regarding difficulty in going to sleep at 2nd week follow up, Levocetrizine in group 2 is significantly effective with 40% patients having zero (0) symptom score in difficulty going to sleep and with mean rank 45.00 as compared to other drugs. At 4th week follow up Montelulast in group 1 is more effective with 60% patients having zero (0) symptom score in difficulty going to sleep and having mean rank 51.30 as compared to other drugs. At 6th week follow up Montelulast in group 1 is more effective with 72% patients having zero (0) symptom score in difficulty going to sleep and having mean rank 49.80 as compared to other drugs.

The Table 3 shows night time awakening symptoms score. It was found that at 2nd week follow up Levocetrizine in group 2 is significantly effective with 40% patients having zero (0) symptom score in Night time Awakening and with mean rank 42.40 as compared to other drugs. At 4th week follow up Montelulast in group 1 is more effective with 60% patients having zero (0) symptom score in night time awakening and having mean rank 51.30 as compared to other drugs. At 6th week follow up Montelulast in group 1 is more effective with 68% patients having zero (0) symptom score in Night time awakening and having mean rank 50.54 as compared to other drugs.

The Table 4 shows nasal congestion on awakening/ obstruction symptom score. It was found that at 2nd week follow up levocetrizine in group 2 is significantly effective with 20% patients having zero (0) symptom score in Nasal congestion on awakening and with mean rank 39.62 as compared to other drugs. At 4th and 6th week follow up montelulast in group 1 is more effective with 44% and 52% patients having zero (0) symptom score in Nasal congestion on awakening and with mean rank 50.20 and 52.58 as compared to other drugs.

The Table 5 shows side effects from day 1 presentation to 6 weeks follow-up. It was found that maximum patients having side effects were seen with chlorpheniramine maleate in group 5. Montelukast Group 1 has no side effects.

Table 2: Showing comparison of difficulty going to sleep symptom score from day 1 presentation to 6 weeks follow-up in five groups.

	Symptom score	Group					Total
		1 Montelukast	2 Levocetrizine	3 Fexofenadine	4 Desloratadine	5 CPM	
Diff. Sleep at day 1 presentation	0	2(8%)	2(8%)	2(8%)	2(8%)	2(8%)	10(8%)
	1	5(20%)	4(16%)	5(20%)	5(20%)	5(20%)	24(19.2%)
	2	14(56%)	16(64%)	14(56%)	14(56%)	14(56%)	72(57.6%)
	3	4(16%)	3(12%)	4(16%)	4(16%)	4(16%)	19(15.2%)
	Total	25	25	25	25	25	125
	Mean Rank	62.98	63.08	62.98	62.98	62.98	
	Sig. #	Chi Square 0.000; p value 1.000; Non Significant					
Diff. Sleep at 2 weeks follow-up	0	5(20%)	10(40%)	4(16%)	5(20%)	2(8%)	26(20.8%)
	1	16(64%)	15(60%)	15(60%)	15(60%)	18(72%)	79(63.2%)
	2	4(16%)	0(0%)	6(24%)	5(20%)	5(20%)	20(16%)
	Total	25	25	25	25	25	125
	Mean Rank	63.42	45.00	69.48	65.40	71.70	
	Sig. #	Chi Square 11.608; p value 0.021; Significant					
Diff. Sleep at 4 weeks follow-up	0	15(60%)	14(56%)	9(36%)	11(44%)	5(23.8%)	54(44.6%)
	1	10(40%)	11(44%)	16(64%)	13(52%)	15(71.4%)	65(53.7%)
	2	0(0%)	0(0%)	0(0%)	1(4%)	1(4.8%)	2(1.7%)
	Total	25	25	25	25	21	121
	Mean Rank	51.30	53.68	65.58	62.16	74.43	
	Sig. #	Chi Square 8.640; p value 0.071; Non Significant					
Diff. Sleep at 6 weeks follow-up	0	18(72%)	14(56%)	13(52%)	13(52%)	7(33.3%)	65(53.7%)
	1	7(28%)	11(44%)	12(48%)	11(44%)	14(66.7%)	55(45.5%)
	2	0(0%)	0(0%)	0(0%)	1(4%)	0(0%)	1(8%)
	Total	25	25	25	25	21	121
	Mean Rank	49.80	59.40	61.80	62.92	73.00	
	Sig. #	Chi Square 6.853; p value 0.144; Non Significant					

DISCUSSION

Allergic rhinitis is the most common atopic disorder seen in the outpatient clinic setting diagnosed by history, physical exam and objective testing.[4] Cysteinyl-leukotrienes (CysLTs) are endogenous mediators of inflammation and play an important role in allergic airway disease by stimulating bronchoconstriction, mucus production, mucosal oedema and inflammation, airway infiltration by eosinophils, and dendritic cell maturation that prepares for future allergic response. *Montelukast* inhibits these actions by blocking type 1 CysLT receptors found on immunocytes, smooth muscle and endothelium in the respiratory mucosa. Initially developed as a treatment for asthma, montelukast has more recently found use in the treatment of allergic rhinitis (AR).[5]

While antihistamines have helped control allergic rhinitis and other allergic disorders successfully, their lack of specificity is responsible for many of their adverse effects. They act primarily on the peripheral H1 receptors and are able to cross the blood brain barrier. Adverse effects attributed to this include marked sedation, central nervous system dysfunction and anticholinergic adverse effects resulting in cognitive function impairment.[6]

The present study was undertaken to evaluate and compare the nocturnal symptoms such difficulty in going to sleep, night time awakening and nasal congestion/obstruction on awakening among allergic rhinitis patients after administration of montelukast, chlorpheniramine meleate, levocetrizine, desloratidine, fexofenadine. The present study found that levocetirizine

provided immediate effect at two weeks which is significantly better than other drugs. But at six weeks, montelukast is best among the drugs which were compared; followed by levocetrizine, fexofenadine, and desloratadine and chlorpheniramine maleate. Montelukast is better drug as it has no significant side effects. Levocetrizine is sedative in few patients and two patients were complaining of headache. Desloratadine

Table 3: Showing comparison of night time awakening symptom score from day 1 presentation to 6 weeks follow-up in five groups.

	Symptom score	Group					Total
		1 Montelukast	2 Levocetrizine	3 Fexofenadine	4 Desloratadine	5 CPM	
N. Awakening at day 1 presentation	0	1(4%)	2(8%)	2(8%)	2(8%)	2(8%)	9(7.2%)
	1	5(20%)	3(12%)	3(12%)	3(12%)	3(12%)	17(13.6%)
	2	15(60%)	17(68%)	16(64%)	16(64%)	16(64%)	80(64%)
	3	4(16%)	3(12%)	4(16%)	4(16%)	4(16%)	19(15.2%)
	Total	25	25	25	25	25	125
	Mean Rank	62.26	61.70	63.68	63.68	63.68	
	Sig. #	Chi Square 0.094; p value 0.999; Non Significant					
N. Awakening at 2 weeks follow-up	0	4(16%)	10(40%)	3(12%)	3(12%)	2(8%)	22(17.6%)
	1	17(68%)	15(60%)	16(64%)	17(68%)	16(64%)	81(64.8%)
	2	4(16%)	0(0%)	6(24%)	5(20%)	7(28%)	22(17.6)
	Total	25	25	25	25	25	125
	Mean Rank	63.00	42.40	69.18	67.12	73.30	
	Sig. #	Chi Square 15.556; p value 0.004; Significant					
N. Awakening at 4 weeks follow-up	0	15(60%)	14(56%)	10(40%)	11(44%)	4(19%)	54(44.6%)
	1	10(40%)	11(44%)	15(60%)	13(52%)	16(76.2%)	65(53.7%)
	2	0(0%)	0(0%)	0(0%)	1(4%)	1(4.8%)	2(1.7%)
	Total	25	25	25	25	21	121
	Mean Rank	51.30	53.68	63.20	62.16	77.26	
	Sig. #	Chi Square 10.105; p value 0.039; Significant					
N. Awakening at 6 weeks follow-up	0	17(68%)	14(56%)	12(48%)	12(48%)	7(33.3%)	62(51.2%)
	1	8(32%)	11(44%)	13(52%)	12(48%)	13(61.9%)	57(47.1%)
	2	0(0%)	0(0%)	0(0%)	1(4%)	1(4.8%)	2(1.7%)
	Total	25	25	25	25	21	121
	Mean Rank	50.54	57.68	62.44	63.62	72.57	
	Sig. #	Chi Square 6.459; p value 0.167; Non Significant					

group had dryness of mouth. Chlorpheniramine maleate has maximum side effects. Six patients who took Chlorpheniramine maleate complained of sedation, one patient complain of psychomotor disturbance. four patients left the study because they discontinued the drug because of sedation. Montelukast, Levocetrizine, Fexofenadine, Desloratadine and Chlorpheniramine maleate resulted in improvement of day time and night time symptoms. Chlorpheniramine maleate had maximum side effects. Fexofenadine, Desloratadine though have less sedating properties, but are not very effective in treatment of nasal obstruction. Levocetrizine provided immediate relief at two weeks but Montelukast was found to be more effective at six weeks treatment.

Gupta et al stated that montelukast serves a role in helping reduce symptoms of allergic rhinitis that are not controlled with antihistamines alone by competitively and reversibly inhibits cysteinyl leukotrienes (CysLTs),

specifically leukotrienes D4 (LTD4), theoretically decreasing congestion and stuffiness associated with allergic rhinitis. Montelukast, as monotherapy has been effective in improving daytime and night time symptoms in patients with allergic rhinitis and in comparison to antihistamines appear to have significantly better improvement in night time symptoms. Nayak et al stated that montelukast currently stands as the most thoroughly tested and prescribed drug that acts through antagonism CysLT1 Rs.[5,7]

Okubo et al conducted a double-blind clinical study to evaluate the efficacy and the safety of Montelukast, a cysteinyl leukotriene receptor one antagonist, 5 mg, 10 mg or placebo orally administered once daily at bedtime for two weeks, to Japanese patients with seasonal allergic rhinitis and reported that the composite nasal symptom score significantly improved in the Montelukast 5mg and 10 mg compared with the placebo group.[8]

Table 4: Comparison of Nasal Congestion on awakening / obstruction symptom score from day 1 presentation to 6 weeks follow-up in five groups.

	Symptom score	Group					Total
		1 Montelukast	2 Levocetrizine	3 Fexofenadine	4 Desloratadine	5 CPM	
N. Congestion at day 1 presentation	1	3(12%)	3(12%)	3(12%)	3(12%)	3(12%)	15(12%)
	2	11(44%)	12(48%)	10(40%)	11(44%)	12(48%)	56(44.8%)
	3	11(44%)	10(40%)	12(48%)	11(44%)	10(40%)	54(43.2%)
	Total	25	25	25	25	25	125
	Mean Rank	63.44	61.24	65.64	63.44	61.24	
	Sig. #	Chi Square 0.312; p value 0.989; Non Significant					
N. Congestion at 2 weeks follow-up	0	1(40%)	5(20%)	2(8%)	2(8%)	1(4%)	11(8.8%)
	1	13(52%)	19(76%)	10(40%)	11(44%)	12(48%)	65(52%)
	2	11(44%)	0(0%)	13(52%)	12(48%)	11(44%)	47(37.6%)
	3	0(0%)	1(4%)	0(0%)	0(0%)	1(4%)	2(1.6%)
	Total	25	25	25	25	25	125
	Mean Rank	67.12	39.62	70.08	67.84	70.34	
	Sig. #	Chi Square 16.339; p value 0.003; Significant					
N. Congestion at 4 weeks follow-up	0	11(44%)	10(40%)	7(28%)	6(24%)	1(4.8%)	35(28.9%)
	1	14(56%)	15(60%)	17(68%)	18(72%)	16(76.2%)	80(66.1%)
	2	0(0%)	0(0%)	1(4%)	1(4%)	4(19%)	6(5%)
	Total	25	25	25	25	21	121
	Mean Rank	50.20	52.50	61.12	63.42	80.95	
	Sig. #	Chi Square 15.660; p value 0.004; Significant					
N. Congestion at 6 weeks follow-up	0	13(52%)	11(44%)	9(36%)	8(32%)	7(33.3%)	48(39.7%)
	1	12(48%)	14(56%)	15(60%)	16(64%)	12(57.1%)	69(57%)
	2	0(0%)	0(0%)	1(4%)	1(4%)	2(9.5%)	4(3.3%)
	Total	25	25	25	25	21	121
	Mean Rank	52.58	57.26	63.40	65.74	66.98	
	Sig. #	Chi Square 3.867; p value 0.424; Non Significant					

Table 5: Side effects from day 1 presentation to 6 weeks follow-up in five groups.

Side effects	1 Montelukast	2 Levocetrizine	3 Fexofenadine	4 Desloratadine	5 CPM
Headache	-	2	1	-	-
Dry Mouth	-	-	1	2	1
Sedation	-	-	-	-	6
Psychomotor Disturbance	-	-	-	-	1

The present study shows that maximum patients were having side effects with Chlorpheniramine maleate in group 5 (six patients were having sedation, one patient having dry mouth and one patient have psychomotor disturbance. In group 4, patient taking desloratadine. Two patients were complaining of dry mouth. In group 3, patients taking Fexofenadine. One patient complained of headache and one patient complained of dry mouth and in

group II, patients taking drug Levocetrizine. Two patients were complaining of headache and in group I, patients taking drug montelukast, no side-effects were reported. Hence in context of side effects, Montelukast is better drug followed by Levocetrizine than Fexofenadine and Desloratidine. Chlorpheniramine maleate has maximum side effects. Four patients taking drug chlorpheniramine maleate in group 5 discontinued the study because of severe side effects.

Levocetrizine does not produce any deleterious effect on psychometric or cognitive functions. However, headaches, dizziness, fatigue and rashes have been reported. The adverse effects of fexofenadine hydrochloride included headache, drowsiness, dizziness, increased appetite with weight gain, and cough.[9]

Older generation antihistamines, such as Diphenhydramine and Chlorpheniramine, are effective at relieving the symptoms of seasonal allergic rhinitis (SAR); however, they are associated with adverse events, including sedation and impairment, at or above the recommended dose. Newer generation antihistamines, such as Desloratidine, Cetrizine and Fexofenadine, were developed to minimize adverse events.[10] Chlorpheniramine and to a lesser extent, newer agents, such as Cetrizine and Azelastine, have been associated with sedation and psychomotor impairment.[11] In a study conducted by Ciebiada et al to investigate the effect of Six week of treatment of persistent allergic rhinitis with Desloratidine, Levocetrizine, or Montelukast alone or with combination. Mean baseline symptom score was 7.7±0.49, 3.74±0.54 after Desloratidine use, 3.6±0.48 after Montelukast use and 3.04±0.4 after Montelukast-Desloratadine use which was found to be statistically significant.[12]

CONCLUSIONS

The present study concludes that in terms of clinical efficacy, safety/tolerability and improvement in night time symptom scores at six weeks therapy in allergic rhinitis, montelukast is the better drug.

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