Olopatadine hydrochloride and rupatadine fumarate in seasonal allergic rhinitis: A comparative study of efficacy and safety

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ABSTRACT

Objective: To compare the efficacy and safety of olopatadine and rupatadine in seasonal allergic rhinitis (SAR). Materials and Methods: A 2-week, single-centered, randomized, open, parallel group comparative clinical study was conducted on patients with SAR. Following inclusion and exclusion criteria, 70 patients were recruited and were randomized to two treatment groups and received the respective drugs for 2 weeks. At follow-up, clinical improvement was assessed in terms of change in total and differential count of leucocytes, serum Immunoglobulin E (IgE) level, Total Nasal Symptom Score (TNSS) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scoring. Results: Both the drugs significantly reduced the differential count \((P<0.001)\) and absolute eosinophil count \((P<0.001)\), but olopatadine was found to be superior. In olopatadine group, there was significantly higher reduction in serum IgE \((P=0.01)\), TNSS \((P<0.001)\) and RQLQ score \((P=0.015)\) than that of rupatadine. Incidence of adverse effects was found to be less in olopatadine group when compared with rupatadine group. Conclusions: Olopatadine is a better choice in SAR in comparison to rupatadine due to its better efficacy and safety profile.

Key words: Seasonal allergic rhinitis, olopatadine, rupatadine, rhinoconjunctivitis quality of life questionnaire scoring, total nasal symptom score

INTRODUCTION

Allergic rhinitis (AR) is one of the most prevalent atopic disorders that affect productivity and quality of life. AR is characterized by sneezing, itching, rhinorrhea, nasal congestion and nasal hypersensitivity, and signs of invasion of nasal mucosa by inflammatory cells.¹ AR includes seasonal AR (SAR), perennial AR (PAR), and PAR with seasonal exacerbations. Prevalence of AR varies from population to population, but on an average, it can affect 25% to 35% of people.² It has a relevant impact on society because of its high prevalence, association with an impaired quality of life, and the presence of co-morbidities.³ Because of the substantial medical care expenditure, the total burden of this disease goes beyond impairment of physical and social functioning.²

Symptoms are produced by inflammatory mediators that are released upon activation of mast cells by antigen-IgE interaction. Histamine is the primary mediator involved in the pathophysiology and this explains the prominent role of histamine H₁-receptor antagonists in the treatment of AR.⁴⁻⁶ Recent studies have proved that platelet-activating factor (PAF)
Two new generation H1-receptor antagonists, olopatadine and rupatadine, are known as dual blockers. Olopatadine hydrochloride is a selective histamine H1-receptor antagonist possessing inhibitory effects on PAF and on the release of inflammatory lipid mediators such as leukotriene and thromboxane from human polymorphonuclear leucocytes and eosinophils. Olopatadine was shown to be highly useful for the treatment of allergic rhinitis, chronic urticaria, and conjunctivitis in double-blind clinical trials. Olopatadine treatment has been claimed to lead to a great reduction of nasal obstruction than other drugs of the same category. Rupatadine fumarate is a selective non-sedating and long-acting oral histamine H1-receptor antagonist that has also been shown to have PAF antagonist activity. It is indicated for use in SAR, PAR, and chronic idiopathic urticaria (CIU) in patients aged 12 years or more. It has a fast onset of action, producing rapid symptomatic relief, and it also has an extended duration of clinical activity which allows once-daily administration.

Though individually olopatadine and rupatadine are efficacious in AR, additional pharmacodynamic activities of these drugs found in some studies indicate a likelihood of differences between these two drugs. The unique effect of rupatadine on interleukins (IL-6, IL-8) and olopatadine on leucotrienes (LTs), thromboxane A2 (TXA2), tachykinin, CC chemokines, leucocyte function-associated antigen 1 (LFA-1) expression has prompted us to design the present study. So this study was conducted to compare the therapeutic efficacy and tolerability of olopatadine and rupatadine in patients suffering from seasonal allergic rhinitis in terms of improvement in Total Nasal Symptom Score (T NSS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)/Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (AdolRQLQ) scoring, serum IgE level, total and differential count of leucocytes, and reported adverse drug reactions.

**MATERIALS AND METHODS**

**Patients**

Seventy patients of SAR attending the department of ear, nose and throat (ENT), Prathima Institute of Medical Sciences, Nagunur, Karimnagar, were enrolled for this study. The study population included patients of either sex, aged between 12-60 years suffering from SAR (a type I immediate hypersensitivity reaction mediated by specific IgE antibody to a seasonal allergen leading to mucosal inflammation characterized by sneezing, itching, rhinorrhea, and nasal blockage) with a past history of SAR (requiring treatment) of 6 months or longer and had documented positive allergy skin test during the previous year. Patients were excluded for the following reasons: Use of concomitant medication(s) that could affect the efficacy of candidate drugs; any existing medical or surgical condition that could affect the metabolism of drugs under study; clinically significant nasal disease (other than SAR) or significant nasal structural abnormalities including nasal polyps; clinically relevant respiratory tract malformations; recent nasal biopsy (within 2 months); nasal trauma; nasal surgery; atrophic rhinitis; rhinitis medicamentosa (within 2 months); or active asthma requiring treatment with inhaled or systemic corticosteroids, routine use of β-agonists, or both; patients with known hypersensitivity to antihistamines; patients with a history of respiratory tract infection or disorder within 2 weeks of the first visit or a respiratory tract infection during first visit; patients who has used antibiotics for acute conditions within 2 weeks of the first visit, or were treated with systemic corticosteroids within 2 months of study initiation, or were treated with topical corticosteroids in concentrations in excess of 1% hydrocortisone for dermatological conditions within 1 month of study initiation. Pregnant and lactating women were also excluded.

**Study design**

The present study is a 2-week, randomized, open label, parallel group comparative clinical study between olopatadine and rupatadine in patients with SAR conducted in a single center. The study was approved by Institute Ethical Committee and procedures followed in this study are in accordance with the ethical standard laid down by Indian Council of Medical Research (ICMR)’s ethical guidelines for biomedical research on human subjects (2006). A written informed consent was taken from all the patients participated in the study after explaining the patient’s diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed treatment (oloapatadine/rupatadine), and the risks and benefits of the alternative treatment. For pediatric subjects, informed consent was obtained from parents or legal guardians.
The study began with a 1-week lead-in period, and patients received placebo capsules. Patients qualified for entry into the lead-in period if they had a TNSS of ≥8 and a nasal congestion score ≥2 over the previous 12 hours (12-hour reflective TNSS). After 1-week lead-in period, eligible participants were randomized by using computer generated random list. After randomization, the patients’ were assigned to one of the following treatment groups:

- Olopatadine group: (n=35 patients) receiving olopatadine 10 mg once daily orally for two weeks
- Rupatadine group: (n=35 patients) receiving rupatadine 10 mg once daily orally for two weeks.

The patients received the drugs free of cost from our institute pharmacy. At the first visit, after detailed history was taken on baseline symptomatology, clinical evaluation (including TNSS, RQLQ scoring) and laboratory investigations (total leucocyte count [TLC], differential count [DC] of leucocytes, absolute eosinophil count [AEC], serum IgE level) were done. Standard interviewer-administered RQLQ was used for patients aged 18 or more and for a patient below 18 years, AdolRQLQ was used. After 2 weeks, all the post drug symptoms were enlisted, baseline laboratory investigations were repeated and clinical improvement was assessed in terms of change in TNSS, RQLQ scoring and laboratory parameters.

**Efficacy outcome measures**

The efficacy variables were changed from baseline to day 14 in the severity of rhinitis symptoms based on TNSS, RQLQ/AdolRQLQ scoring, serum IgE level, TLC and DC of leucocytes. TNSS was considered as the primary outcome of the study.

Symptom severity was determined by the TNSS which consisted of runny nose, sneezing, nasal itching, and nasal congestion scored on a severity scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe), such that the maximum possible TNSS is 24. To be eligible for entry into the treatment period, patients must have recorded a morning or evening TNSS ≥8 on at least 3 days during the lead-in period and a morning or evening nasal congestion score of 3 on at least 3 days. [5,19,20]

The RQLQ is a disease-specific, validated quality-of-life questionnaire developed for the measurement of physical, emotional, and social problems common to adults and children with allergies. The version of the RQLQ administered depended on patient age, with patients below 18 years assessed with the adolescent RQLQ (AdolRQLQ) and patients 18 years and older assessed with the standard version RQLQ. Patients rated experiences over the past week for questions related to activities, sleep, practical problems, nasal symptoms, eye symptoms, emotions, and non–hay fever symptoms. [17,18]

TLC and DC was done by hemocytometer and IgE level was estimated by chemiluminescent immunoassay.

**Safety measures**

Tolerability was assessed in terms of reported adverse experiences and vital signs which were measured at baseline and at the end of the study. All reported adverse drug reactions were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) and compared between the groups. [21]

**Statistical analysis**

The statistical calculation for the paired \( t \)-test, unpaired \( t \)-test and Fisher’s test were done by statistical software Instat+ 3.036 (Statistical Services Centre, University of Reading, Reading, England). A ‘ \( P \) value’ of <0.05 (2-tailed) was considered statistically significant. The statistician was blinded to the groups during analysis. Considering TNSS as primary outcome, sample size has been calculated taking level of significance (\( \alpha \)) = 0.05, power of the study (1- \( \beta \)) = 0.85 and expected mean difference 2.5.

**RESULTS**

**Patient disposition and baseline demographics**

Seventy patients of SAR were recruited and randomized to two treatment groups to receive either olopatadine (\( n=35 \)) or rupatadine (\( n=35 \)). Post-baseline values are missing in 13 patients as we have lost 13 patients (7 in rupatadine group and 6 in olopatadine group) in follow-up due to non-compliance [Figure 1]. The baseline demographic data and clinical characteristics of all 70 patients participated in this study have been compared in the Table 1 and \( P \) values suggest that there is no statistically significant difference in between the study groups in the parameters studied in the first visit. This proves the homogeneity of our study subjects in two groups. The patients ranged in age from 12 to 60 years (mean age, 37.6 years); 54% were female and 46% were male; the average duration of SAR was 15.4 months.

**Efficacy analysis**

**Change in total and differential count**

TLC and DC were done both at first and second visit in both study groups. The results in the Table 2 reveal that there was mean difference of 262 in TLC in olopatadine group in comparison to 200 in rupatadine group. Similarly, there was a mean decrease of 0.9 in DC neutrophil in olopatadine group in comparison to mean decrease of 1.0 in rupatadine group. The changes in both the parameters in study groups were not statistically significant and when the mean differences in two groups were compared by \( t \)-test, the change was not found to be statistically significant.

There was a mean decrease of 2.04 in DC eosinophil and in
206 in AEC olopatadine group. In rupatadine group, it was 1.21 and 117 in DC eosinophil and AEC, respectively. The changes of both DC eosinophil and AEC in both rupatadine and olopatadine group were found to be statistically significant and when the mean differences in two groups were compared by t-test, the change in olopatadine group was found to be statistically significant [Table 2].

Change in serum IgE level
In olopatadine group, there was a mean reduction of 36.4 in IgE in comparison to 16.5 in rupatadine group. The individual changes in both the groups were statistically significant. The comparative analysis of the mean difference in individual group also revealed to be statistically significant ($P=0.01$) [Table 2].

Change in total nasal symptom score
The results shown in the Table 2 reveal that there was a mean decrease of 6.5 in TNSS in olopatadine group whereas it was 2.7 in rupatadine group and these changes in individual groups were statistically significant. The comparison of the mean differences also found to be statistically highly significant ($<0.001$).

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**Table 1: Baseline demographic data and clinical characteristics of the patients participated in the study in the first visit**

| Characteristics                              | Olopatadine Group [n=35] | Rupatadine Group [n=35] | P value |
|----------------------------------------------|--------------------------|--------------------------|---------|
| Number of patients recruited                 | 35                       | 35                       |         |
| Number of patients at follow-up              | 29                       | 28                       | 0.81    |
| Female sex (%)                               | 57.1                     | 51.4                     |         |
| Age (years)                                  | 36.5 ± 12.9              | 38.7 ± 14.2              | 0.49    |
| Duration of suffering (months)               | 16.1 ± 7.9               | 14.8 ± 7.2               | 0.49    |
| Total Leucocyte Count                        | 9349 ± 1380              | 8877 ± 1404              | 0.16    |
| DC Neutrophil (%)                            | 63.2 ± 4.6               | 64.5 ± 3.7               | 0.22    |
| DC Eosinophil (%)                            | 7.4 ± 1.5                | 7.7 ± 1.7                | 0.51    |
| Absolute Eosinophil Count (cells per microlitre) | 699 ± 191              | 684 ± 200                | 0.75    |
| IgE (IU/ml)                                  | 325.1 ± 77.6             | 321.9 ± 76.7             | 0.86    |
| Total Nasal Symptom Score                    | 16.2 ± 3.2               | 14.9 ± 3.2               | 0.10    |
| Rhinocconjunctivitis Quality of Life Questionnaire (RQLQ) scoring | 3.7 ± 1.1               | 3.3 ± 0.8               | 0.11    |

Data are in Mean ± SD
By considering 25% decrease in TNSS as clinically significant, we found that 25 patients in olopatadine group and 17 patients in rupatadine groups showed clinically significant improvement. These findings was put in 2X2 contingency table and tested by Fischer’s test which was found to be statistically significant ($P=0.038$).

### Change in Rhinoconjunctivitis quality of life questionnaire score

The changes in the Change in Rhinoconjunctivitis quality of life questionnaire (RQLQ) score has been represented in the Table 2 which shows that there was a mean decrease of 0.67 in olopatadine group in comparison to 0.40 in rupatadine group. Both these changes were found to be statistically significant. When the mean differences in two groups were compared by $t$-test, the change in rupatadine group was found to be statistically significant ($P=0.015$).

### Safety analysis

Both the drugs were well tolerated without any new/unpredictable/alarming side effects. In rupatadine group, one patient complained of drowsiness. Fatigue and headache were complained by one patient in each group. Dryness of mouth was complained by one patient of rupatadine group. Overall incidence of adverse effects was 6.9% in olopatadine group whereas 14.3% in rupatadine group. According to CTC grading of adverse drug reactions (CTC version 2.0), all the reported side effects were of grade 1 (mild). To compare the incidence of adverse effects of two groups, Fischer’s Exact test was done and it was found to be statistically non-significant ($P=0.42$).

### DISCUSSION

Treating the symptoms of SAR and ensuring a decent quality of life to the patients is challenging to the physicians. An increasing understanding of the pathomechanisms in the last few decades has revealed the potentiality of the new generation antihistaminics with dual blocking property in the treatment of AR. Rupatadine and olopatadine have already known to be effective in AR in several clinical trials, but this is the pilot study to compare their efficacy and safety and thus to choose the better agent.

This out-door based study has been conducted in a tertiary care center on a population which is homogenous with minimum ethnic variation. As most of the patients gave history of the disease for at least two consecutive seasons when rhinitis aggravates, we have chosen the winter months for conducting this study.

The association between eosinophils and allergic disease has been known for many years. The effector functions of eosinophils appear to be derived primarily from release of lipid mediators and proteins, including cytokines and granule...
proteins. Any allergic condition usually affects the percentage of eosinophil and its absolute count and probably that is the reason why the effects of the drugs have not been directly reflected on TLC and neutrophil count. Increase in eosinophil count is the hallmark of late phases of allergic rhinitis and olopatadine has shown a superior control on this hematological parameter in comparison to rupatadine. Atopic individuals can have IgE levels raised up to 10 times the normal value. On exposure to a nasal allergen, circulating IgE levels increases and remains elevated 2 weeks after the initial provocation. As allergic rhinitis is an IgE mediated immunological response, treatment with olopatadine proved to be better than rupatadine by reducing IgE level significantly.

The primary goal of treating SAR patients is to give symptomatic relief. So a significant decrease in TNSS has prognostic importance and olopatadine was found to have edge over rupatadine. As AR is a condition that markedly affects quality of life, ensuring a decent quality of life and reduction of RQLQ score is mandatory. In this study, olopatadine has been proved to be superior to rupatadine by decreasing RQLQ score significantly.

Rupatadine and olopatadine both are known to be dual blockers i.e. other than their antihistaminic property, they can antagonize PAF also and that is the reason why both the drugs are highly effective in AR. The difference in their efficacy is due to their varied pharmacodynamic effects. Rupatadine has a high H1 receptor binding affinity which allows the molecule to inhibit the histamine-induced interleukin (IL)-6 and IL-8 production using concentrations that are below the plasma levels reached at therapeutic dose.[1][22] Similarly, olopatadine has additional pharmacological actions which are beneficial in the treatment of AR. The probable superiority of olopatadine may be attributed to the following findings in previous studies: (1) Olopatadine can reduce the amount of cell-associated PAF by 52.8%. [10] (2) Olopatadine suppresses LTs and TXA2 release and PAF formation by reducing arachidonic acid release from membrane phospholipids, probably through interference with phospholipase A2 (PLA2).[10,13] (3) Miyake et al., reported that olopatadine inhibited the release of peptide LTs from human eosinophils.[13] (4) Olopatadine inhibited the histamine-enhanced expression of intercellular adhesion molecule (ICAM)-1 and E-selectin.[23] (5) Olopatadine inhibited histamine-induced increase in intracellular calcium concentration in cultured guinea pig tracheal smooth muscle cells.[19,20] (6) Olopatadine also antagonized histamine induced phosphoinositide turnover in cultured human conjunctival epithelial cells, human corneal fibroblast and transformed human trabecular meshwork cells.[12,24] (7) Olopatadine inhibited antigen-induced histamine release from sensitized rat peritoneal exudate cells and rat basophilic leukemia cells.[25,27] (8) Olopatadine also inhibited anti-human IgE-induced histamine release from human conjunctival tryptase/chymase-containing mast cells.[27] (9) Olopatadine showed inhibitory effects on tachykinin release from sensory nerve endings in isolated guinea pig bronchi and in vivo various experimental allergic models.[10,14] (10) Olopatadine inhibited the release of CC chemokine production in human nasal epithelial cells (HNECs).[15] (11) Olopatadine dose-dependently repressed the IL-5-induced expressions of CD11a/CD18 (Leukocyte Function-associated Antigen-1: LFA-1) and CD11b/CD18 (Mac-1) on rat peritoneal eosinophils suggesting that olopatadine may inhibit antigen-induced eosinophil infiltration through repression of LFA-1 and Mac-1 expression.[16] (12) Olopatadine has been shown to suppress the activity of S100A12 which is a member of the S100 family of calcium-binding proteins, and exerts multiple proinflammatory activities including chemotaxis for monocytes and neutrophils.[28]

**CONCLUSIONS**

From the analysis of present comparative clinical study between olopatadine and rupatadine, we can conclude that olopatadine is a better choice in seasonal allergic rhinitis in comparison to rupatadine due to its better efficacy and safety profile. Non-blinding being its limitation, the findings of this exploratory pilot study can be confirmed by multicentric, randomized, double-blind large population studies.

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