

A Review of Rupatadine in the Treatment of Seasonal Allergic Rhinitis

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Abstract: Allergic rhinitis is a common condition that affects 10%–20% of general population. Seasonal allergic rhinitis is a subset of allergic rhinitis mediated by histamine, proteases, leukotrienes, prostaglandins, platelet-activating factor (PAF) and cytokines. These mediators are released from mucosal mast cells which degranulate after cross linking of pollen with mast cell-bound specific IgE. Due to its selective anti H1, antiPAF and anti pro inflammatory properties, rupatadine represents an effective treatment of seasonal allergic rhinitis symptoms. It is a once a day antihistamine and exhibits a sustained 24-hour effect. Rupatadine reduces effectively the nasal obstruction, one of main symptoms of seasonal allergic rhinitis. It is a nonsedating antihistamine, does not impair driving performance and has no proarrhythmic effect, even in supra therapeutic doses. Long term safety of rupatadine 10 mg daily has been established. Rupatadine is a sound first line antihistamine for treatment of seasonal allergic rhinitis.

Keywords: rupatadine, seasonal, allergic, rhinitis, treatment, antihistamines

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Introduction

Rhinitis is a chronic condition that is characterized by inflammation of the nasal mucosa.¹ Allergic rhinitis is the most common cause of rhinitis. Allergic rhinitis represents a global health problem affecting 10% to 20% of the population and approximately 500 million patients globally.²

Seasonal allergic rhinitis is characterized by the onset of rhinorrhea, sneezing, nasal stuffiness and itchy palate which correlate with the onset of exposure to seasonal pollen(s). A great proportion of patients experience associated allergic eye symptoms such as red, itchy and teary eyes and lower respiratory symptoms indicative of bronchial hyper reactivity and/or seasonal induced asthma. Taking into consideration the severity of symptoms, the allergic rhinitis was classified into Mild and Moderate/Severe.^{3,4} Patient who experience troublesome symptoms affecting their daily activities, work/school performance and impeding them from participating in sport and leisure activities are considered having a Moderate/Severe allergic rhinitis as compared to patients who are only mildly affected. The duration of symptoms for more than 4 days per week and for 4 weeks consecutively defines persistent versus intermittent allergic rhinitis. In addition to the ARIA classification of allergic rhinitis, the term seasonal allergic rhinitis includes a separate condition characterized by the sudden onset of symptoms which correlate with the exposure to seasonal pollen(s) and confirmed by positive IgE mediated tests, skin and/or specific IgE.

Treatment of allergic rhinitis combines allergen avoidance (when possible), pharmacotherapy, immunotherapy and education.³ Since allergen avoidance can be practically difficult to implement in seasonal allergic rhinitis, the pharmacological treatment of seasonal induced symptoms represents an effective treatment strategy. Amongst pharmacological options for symptomatic treatment of allergic rhinitis, ARIA guidelines recommend the use of second-generation nonsedating oral H1 antihistamines.^{3,4} Rupatadine is a relatively new oral second generation antihistamine with anti H1, anti PAF and anti proinflammatory properties.^{5,6} This review considers the use of rupatadine in the treatment of seasonal allergic rhinitis.

Methods

A literature search was conducted using Medline (Ovid) and Pubmed. Search terms used were:

“rupatadine”, “allergic “rhinitis”, “seasonal”, “pathophysiology”, “cognition”, “cardiac effects”, “safety”, “driving”, “guidelines”. The search was limited to English literature only. Human studies and reviews on allergic rhinitis, its pathophysiologic mechanisms, classification, current treatment guidelines focusing on pharmacological management, were reviewed. Human studies on the role of rupatadine in the treatment of seasonal allergic rhinitis, its safety and tolerance were included. Studies and reviews on treatment of other allergic conditions with rupatadine were not included, unless they were used to explain the mechanisms of action of rupatadine or its safety features.

Antihistaminic and Anti PAF Properties

The basic immunologic mechanism of seasonal allergic rhinitis includes release of mediators from mast cells (MCs) after pollen allergen interaction with specific cell-bound IgE. The mediators include vasoactive amines (eg, histamine), proteases, lipid-derived mediators such as leukotrienes, prostaglandins, platelet-activating factor (PAF) and cytokines. It has been shown by Vasiadi et al that rupatadine can inhibit histamine and cytokine secretion (IL6, IL8, vascular endothelial growth factor, etc) from human mast cells in response to allergic, immune and neuropeptide triggers.⁷ These actions endow rupatadine with unique properties in treating allergic inflammation.

The antihistaminic properties of Rupatadine have been established in animal and human studies. Studies in humans have demonstrated a clear efficacy of rupatadine versus placebo in reducing seasonal allergic nasal symptoms. Subjective single and composite nasal and nonnasal symptoms were consistently less severe with rupatadine use than with placebo use throughout a 6-hour Vienna Chamber challenge, with the most significant effects noted for nasal rhinorrhea, nasal itching, and sneezing attacks ($P < 0.001$ for all variables). Other symptoms such as nasal congestion, mean secretion weights and overall feeling of complaint were also significantly reduced with active treatment compared with placebo use ($P < \text{or} = 0.005$ and $P < \text{or} = 0.001$, respectively).⁸

Clinical efficacy outcomes of Rupatadine in the treatment of allergic rhinitis were compared with placebo and other antihistamines such as cetirizine, ebastine and loratadine. These studies have looked at



the mean total daily symptom score (mTDSS) which was based on the daily subjective assessment of the severity of each rhinitis symptom—nasal (runny nose, sneezing, nasal itching and nasal obstruction) and non-nasal (conjunctival itching, tearing, and pharyngeal itching)—recorded by patients in their diaries. In a randomised, double-blind, parallel-group, multicentre clinical trial, the efficacy and safety of rupatadine compared to cetirizine in the treatment of patients with seasonal allergic rhinitis (SAR) were evaluated.¹⁰ A total of 249 patients were randomised to receive rupatadine 10 mg once daily (127 patients) or cetirizine 10 mg (122 patients) for two weeks. The mTDSS was 0.7 for both treatment groups (intention to treat analysis). In the investigator's global evaluation of efficacy at the seventh day of treatment, 93.3% and 83.7% patients in the rupatadine and cetirizine groups, respectively, showed some or great improvement ($P = 0.022$). In the per protocol analysis ($n = 181$), runny nose at the seventh day of treatment was absent or mild in 81.1% of patients in the rupatadine group and in 68.6% of patients in the cetirizine group ($P = 0.029$), although the statistical significance was not maintained at the end of second week.

Similar efficacy outcomes were measured in another multicentre double-blind, randomized, parallel-group and placebo-controlled study including 250 patients with SAR.¹¹ Patients were randomized to receive either rupatadine 10 mg, ebastine 10 mg or placebo once daily for 2 weeks. This study demonstrated significant differences in mDTSS between rupatadine and placebo (33% lower for rupatadine group; $P = 0.005$) after 2 weeks of treatment. The total symptoms score (TSS) for rupatadine was 22% lower than for ebastine, although the differences were not statistically significant.

Efficacy of rupatadine 10 mg and 20 mg administered once-daily for two weeks was compared with that of loratadine 10 mg in the treatment of seasonal allergic rhinitis in a randomized, double-blind, parallel-group, comparative study.¹² This study involved a total of 339 SAR patients who were randomized to receive rupatadine 20 mg (111 patients), rupatadine 10 mg (112 patients) or loratadine 10 mg (116 patients). The mTDSS was significantly lower in the groups treated with rupatadine 20 mg (0.80 ± 0.46) and rupatadine 10 mg (0.85 ± 0.52) than in the group

treated with loratadine 10 mg (0.92 ± 0.51) by protocol analysis ($P = 0.03$) but not by intention-to-treat analysis. The secondary variables also demonstrated significantly milder symptoms in patients treated with rupatadine 20 mg and rupatadine 10 mg, particularly the sneezing and nasal itching.

Reduction of Nasal Obstruction

Objective assessment of severity of allergic rhinitis includes symptom scores, measurement of nasal obstruction with acoustic rhinometry and determination of nitric oxide levels in nasal lavage, cytology or nasal biopsy.³ Valero et al, measured the effect of rupatadine 10 mg daily taken for 3 consecutive days in reducing nasal volume in 30 asymptomatic patients with seasonal allergic rhinitis in a double blind, placebo controlled, crossover study.⁹ Patients underwent a nasal allergen challenge and nasal volumes and nitric oxide levels were obtained at baseline and at 2 and 24 hours post challenge. Nasal airway blockage measured with acoustic rhinometry was significantly lower in the rupatadine group than in the placebo group (47%, $P < 0.05$) at 2 hours postchallenge which correlated with the decrease in mean total symptoms score compared with placebo at the same time point.

Sustained 24-hour Effect

Similarly to other inflammatory conditions, symptoms of allergic rhinitis have been shown to follow a pattern of circadian rhythm.¹³ Previous studies have shown that severity of symptoms of allergic rhinitis is typically greatest in the morning for all major symptoms, including runny nose, sneezing, and nasal congestion. Possible explanations for increased morning symptoms include increased levels of histamine and other inflammatory mediators.¹⁴ Therefore, the effective relief of morning symptoms represents an important consideration in the pharmacologic treatment of allergic rhinitis. Morning and evening efficacy evaluations of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis in a randomized, double-blind, placebo-controlled trial was reported by Marmouz F, et al.¹⁵ The main outcome studied was the morning/evening reflective total symptom score (5TSS) over the treatment period. This study demonstrated that at morning evaluation, there was a significant reduction from baseline for 5TSS with rupatadine 10 mg (-36.8% , $P < 0.01$) and



20 mg (-46.3% , $P < 0.01$) compared with placebo. Moreover, when individual symptoms were assessed, statistically significant differences for rhinorrhea ($P < 0.01$), nasal itching ($P < 0.01$), and sneezing ($P < 0.01$) were shown in all active groups compared with placebo at morning and evening evaluations. Overall, rupatadine was found to have a sustained 24-hour effect over a 4 week period.

Safety Studies

Safety of rupatadine has been looked at several clinical studies. Picado summarized the adverse effects in 2025 subjects exposed to rupatadine 10 mg in controlled clinical trials. Somnolence, headache and fatigue were the most common adverse events reported at a rate of 9.5%, 6.8% and 3.2%, respectively. The reported adverse events were not significantly different from placebo which caused somnolence, headache, fatigue at a rate of 3.4%, 5.6% and 2%, respectively.¹⁶ The long term safety profile of rupatadine 10 mg daily taken for 12 months was examined in an uncontrolled study of 120 patients with persistent allergic rhinitis according to European Medicine Agency guidelines. The more frequent treatment-related adverse effects during this period were somnolence (6%) and headache, dry mouth, fatigue and rash ($<1\%$).¹⁷ Moreover, same study concluded that detailed ECG assessments demonstrated no clinically relevant abnormal ECG findings, nor any QTcB increases >60 msec or QTcB values >470 msec for any patient at any time during treatment.

Cardiac Safety

The previous cardiac safety experience demonstrated in several clinical trials, was confirmed by a 'thorough QT/QTc study' performed by Donado E, et al and according to the International Conference on Harmonization guidelines.¹⁸ It involved a randomized (gender-balanced), parallel-group study including 160 healthy volunteers. Healthy volunteers received Rupatadine, 10 and 100 mg per day, and placebo in a single-blind fashion for 5 days, whilst moxifloxacin 400 mg per day was given on days 1 and 5 in an open-label fashion as positive control. Cardiac monitoring was performed by intermittent (10 seconds) and continuous ECG monitoring at baseline and on treatment days. The ECG data analysis for both rupatadine treatments showed no signal effects on the ECG,

after neither single nor repeated administration, whilst moxifloxacin-positive control group produced the expected change in QTcI duration (around 5 ms). This study concluded that rupatadine had no proarrhythmic potential at therapeutic and suprathreshold doses and raised no concerns regarding its cardiac safety.

Cognition Safety

One of the main concerns regarding the use of antihistamines for treatment of allergic rhinitis is the ability to cause negative effects on cognition or psychomotor performance. Rupatadine does not easily cross the blood-brain barrier and has been considered a non-sedating antihistamine at therapeutic doses.^{5,6} The lack of sedation effect has been examined in several studies. The effect of rupatadine on driving performance was studied in a double-blind, three-way crossover study which compared the acute effects of rupatadine, relative to placebo and hydroxyzine (as an active control), on healthy subjects' driving performance.¹⁹ Twenty subjects received a single dose of rupatadine 10 mg, hydroxyzine 50 mg, or placebo in each period of this randomized, double-blinded three-way crossover study. Two hours postdosing, the study subjects operated a specially instrumented vehicle in tests designed to measure their driving ability. Before and after the driving tests, the ratings of sedation were recorded. This study showed no significant difference between rupatadine and placebo in the primary outcome variable: standard deviation of lateral position (SDLP); however, hydroxyzine treatment significantly increased SDLP ($P < 0.001$ for both comparisons). Objective (Stanford sleepiness scale) and subjective sedation ratings (Visual Analogue Scales) showed similar results: subjects reported negative effects after hydroxyzine but not after rupatadine. Additionally, the effects of different doses of rupatadine on central nervous system in 18 healthy young subjects of both sexes, in a crossover, randomised, double-blind, placebo-controlled study, have been reported.²⁰ Study participants received rupatadine 10 mg, 20 mg, 40 mg, 80 mg and hydroxyzine 25 mg as positive control. Using the global nonparametric Friedman test changes from placebo in 15 objective variables from psychomotor performance, this study concluded that rupatadine displayed a psychomotor impairment activity only at the highest dose (80 mg), while the therapeutically relevant lower doses (10 and 20 mg) were similar to placebo. Similarly, therapeutic dose of rupatadine (10 mg) did



not augment the cognitive and psychomotor impairment effects caused by simultaneous alcohol intake.

Conclusion

Allergic rhinitis is a common condition of children and adults that, although not life-threatening, can significantly impair quality of life and cause increased direct and indirect health care costs.^{21,22} A recently published analysis determined that patients with allergic rhinitis averaged 3 additional office visits, 9 more prescriptions filled, and \$1500 in incremental healthcare costs in 1 year than similar patients without allergic rhinitis.²³ Treatment of symptoms of allergic rhinitis will improve patients' performance and quality of life, and reduce overall health care related costs.

Seasonal allergic rhinitis is a subset of allergic rhinitis caused by exposure to pollen(s) leading to mucosal mast cell degranulation and release of mediators causing allergic inflammation. Rupatadine is a nonsedating, selective antihistamine with antiPAF properties. The dual action is a unique property of rupatadine amongst other nonsedating antihistamines. Rupatadine is a once a day antihistamine and was found to have a sustained 24 hour effect. Rupatadine effectively reduces nasal obstruction in patients suffering from seasonal allergic rhinitis symptoms. In treatment of seasonal allergic rhinitis, rupatadine 10 mg and 20 mg was found to be significantly better than placebo and similarly effective as other non sedating antihistamines such as cetirizine, sebastine and loratadine, with probable faster effect in controlling allergic rhinitis symptoms than cetirizine. Long term safety profile of rupatadine 10 mg over 12 months has been established. It has no proarrhythmic potential and does not affect driving performance. Rupatadine represents a sound first line antihistamine for treatment of seasonal allergic rhinitis.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration

nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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