Evaluation of Morning and Evening Nasal Symptoms Scores of Allergic Rhinitis: A Pooled-Analysis of Rupatadine Randomized Placebo-Controlled Clinical Trials

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1 Introduction

Many inflammatory diseases exhibit variations in symptoms over time. Specifically, symptoms of allergic rhinitis (AR) have been shown to follow a pattern of circadian variation (Storms, 2004). Thus, severity of symptoms of AR is typically greater in the morning for all major symptoms, including nasal blockage, runny nose and sneezing, in approximately 70% of patients (Haye et al., 2005). Possible causes of increased morning symptoms include increased levels of histamine and other inflammatory mediators (Aoyagi et al., 1999). Patients report that morning symptoms have a negative impact on quality of life throughout the rest of the day. Therefore, an important consideration in the pharmacologic treatment of AR is the effective relief of morning symptoms.

Second-generation oral antihistamines are among the most widely prescribed agents due to their effectiveness in the treatment of allergic diseases. Although newer long-acting antihistamine preparations permit once-daily dosing, many patients with AR experience breakthrough symptoms and a reduction of clinical efficacy at the end of the dosing interval. Most antihistamines demonstrate a peak effect approximately 5 to 7 hours after oral administration, and the duration varies depending on the half-life of parent compound and active metabolites (Brunton, 2002).

The aim of this study was to evaluate the overall efficacy of rupatadine, an anti-H$_1$ and PAF antagonist compound (Keam & Plosker, 2007; Merlos et al., 1997; Mullol et al., 2008), in the control of morning and evening nasal symptoms in patients with allergic rhinitis.

2 Methods

This analysis includes the pooled data from five randomized, double blind, placebo-controlled studies previously published as separate trials (Fantin et al., 2008; Guadaño et al., 2004; Izquierdo et al., 2000; Lukat et al., 2013; Marmouz et al., 2011). These studies had approximately the same number of patients as well as a similar study design, which makes the pooled analysis appropriate. The only difference among the studies was the treatment duration, which was longer (12 weeks) for one study in Perennial AR (PAR) compared to the 2 and 4-week duration for the rest of the trials. All patients received 10 mg od (1 tablet rupatadine) or placebo od, both tablets had the same appearance and were packaged identically.

2.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were very similar between trials. Patients aged ≥ 18 years old with a diagnosis of AR for at least 12 months, and with a total nasal symptom score ≥ 5 (out of a possible total score of 12) were included in the study. During a screening visit, the patients must show a positive skin prick test (diameter of the papule > 3 mm compared to saline solution control, or ≥ to that obtained with histamine at a 10 mg/mL dilution) at inclusion or within one year before inclusion. The allergens used in the prick test are usually related to PAR or SAR. A normal 12-lead ECG had to be documented at the pre-screening visit with the following requirements: QTc < 430 msec for males, and QTc < 450 msec for females. Women of childbearing age had to show a negative pregnancy test and had to use contraceptive measures during the study.

Patients suffering from non-allergic rhinitis (e.g. vasomotor, infectious or drug-induced rhinitis) or with a negative prick test were not included. Treatments with nasal descongestants in the previous 24 hours, oral antihistamines or disodium chromoglycate (previous week), ketotifen (previous month), topi-
cal antihistamines (previous 48 hours), systemic or topical treatment with corticosteroids (except for to

cipical hydrocortisone < 1%), immunosuppressants, or any investigational drug taken within 2 weeks prior to

inclusion were considered as exclusion criteria. Other relevant exclusion criteria included abnormal lab

oratory values (including hematology and blood chemistry tests) of clinical significance, certain condi-

tions that may interfere with response to treatment such as mild asthma treated with inhaled bronchodila-

tors or inhaled corticosteroids (> 800 mcg/day of budesonide or beclomethasone, or > 500 mcg/day of

fluticasone), obstructive nasal polyps or hypersensitivity to compounds structurally related to the study
drug.

2.2 Evaluation of Efficacy

In order to compare across studies, the primary endpoint variable was defined as the mean change from

baseline of total reflective symptoms’ score (T4SS) at 2, 4, 8 and 12 weeks of treatment duration. We

used the total nasal symptoms’ score since this has been suggested to be a much more appropriate mea-

sure for allergic rhinitis symptoms assessment (European Medicines Agency, 2005). T4SS consists of a

composite score of the severity scores for four AR symptoms (runny nose, itchy nose, blocked nose and

sneezing), which were recorded in patient dairy cards. Each symptom was scored 0-3 (with 0=absent, 1=mild,

2=moderate, or 3=severe) twice daily, in the morning (AM) within 1 h of awakening and prior to
drug intake and in the evening (PM), around 12 h later. Both the AM and PM symptom severity were

assessed in a reflective manner (over the previous 12 h).

Additional the safety of treatments were evaluated accordingly to the incidence of adverse events

(AEs) recorded in the patient’s diaries. All AEs were coded using the same MedDRA dictionary across

all clinical studies.

Daily AM/PM symptoms scores were analyzed from a fixed effect model, weighting the average

of each study scores by its individual variance and the subject evaluation was carried out with Cochran's

Mantel-Haenszel test. All statistical procedures were performed using SAS® software version 9.1 for

Windows (SAS Institute Inc. Cary, NC USA). All tests of significance were carried out at a 0.05 level.

3 Results

Table 1 summarizes the main features of the five controlled clinical trials included in this pooled analysis.

A total of 1017 patients (RUP=511; PBO=506) were included in the pooled analysis at baseline score.

Rupatadine showed a significant reduction of symptoms’ score at AM and PM evaluations. The

mean change from baseline over 2, 4, 8 and 12 weeks of the TSS morning (AM) evaluations showed

significant improvements (p < 0.001) in the ANOVA comparison with placebo group (see Figure 1).

Reductions from baseline of -35%, -40%, -49% and -55% were obtained at 2,4,8, and 12 weeks respec-
tively. Similarly, the mean change from baseline of the TSS evening (PM) evaluations were also signifi-
cant (p < 0.001) at 2 (-32%), 8 (-41%) and 12 (-49%) weeks, with the exception of 4 (-41%) weeks,

which was not significant (see Figure 2).

When individual symptoms were assessed, statistically significant improvement for runny nose

was detected in the morning (AM) evaluation at 2 (p < 0.001), 4 (p < 0.05), 8 (p < 0.001) and 12 (p <

0.001) weeks (see figure 3a). The evening (PM) evaluations showed only significant improvement for
this symptom at 2 (p < 0.001) and 12 (p < 0.001) weeks (see figure 3b). The itchy nose showed statisti-
cally significant improvements at any time: 2 (p < 0.001), 4 (p < 0.05), 8 (p < 0.001) and 12 weeks (p <
Figure 1: 4TSS morning (AM evaluation). Mean change from baseline over 2, 4, 8 and 12 weeks.

Figure 2: 4TSS evening (PM evaluation). Mean change from baseline over 2, 4, 8 and 12 weeks.

Figure 3: Runny nose. (a) Morning: AM evaluation; (b) Evening: PM evaluation. Mean change from baseline over 2, 4, 8 and 12 weeks.
<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Allergic Rhinitis</th>
<th>N Patients</th>
<th>Duration (weeks)</th>
<th>Study Design / Level of Evidence</th>
<th>Age (Years) Mean ± sd</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupatadine 10 mg od</td>
<td>SAR</td>
<td>178</td>
<td>2</td>
<td>m, r, db, pg, Level 2</td>
<td>35 ± 12.7</td>
<td>Izquierdo et al., 2000</td>
</tr>
<tr>
<td>Rupatadine 20 mg od Placebo od</td>
<td>SAR</td>
<td>250</td>
<td>2</td>
<td>m, r, db, pg, Level 2</td>
<td>33 ± 10.1</td>
<td>Guadaño et al., 2004</td>
</tr>
<tr>
<td>Rupatadine 10 mg od Ebastine10 mg od Placebo od</td>
<td>SAR</td>
<td>379</td>
<td>4</td>
<td>m, r, db, pg, Level 2</td>
<td>31 ± 12.7</td>
<td>Lukat et al., 2013</td>
</tr>
<tr>
<td>Rupatadine 10 mg od Desloratadine 5 mg od Placebo od</td>
<td>PAR</td>
<td>282</td>
<td>4</td>
<td>m, r, db, pg, Level 2</td>
<td>32 ± 10.9</td>
<td>Marmouz et al., 2011</td>
</tr>
<tr>
<td>Rupatadine 10 mg od Cetirizine10 mg od Placebo od</td>
<td>PER</td>
<td>543</td>
<td>12</td>
<td>m, r, db, pg Level 2</td>
<td>29 ± 12.9</td>
<td>Fantin et al., 2008</td>
</tr>
</tbody>
</table>

Table 1: SAR; seasonal allergic rhinitis; PAR, perennial allergic rhinitis; PER persistent allergic rhinitis ; m, multicentre; r, randomized, db, double-blind, pg, parallel groups, od, once daily.

0.001) (see figure 4a). On the contrary when the PM evaluation was analyzed, the improvement was significant only the first 2 weeks (p < 0.001) (see figure 4b). Nasal obstruction was also evaluated at morning achieving clear significant improvements at 2 (p < 0.001), 4 (p < 0.001), 8 (p < 0.001) and 12 weeks (p < 0.001) (see figure 5a). The evening evaluations for blocked nose showed an important and consistent improvement at 2 (p < 0.001), 4 (p < 0.001), 8 (p < 0.001) and 12 weeks (p < 0.01) as well (see figure 5b). The last symptom evaluated was sneezing, which is one of the most common symptoms in AR. The morning evaluations showed significant improvements at 2 (p < 0.001), 4 (p < 0.001), 8 (p < 0.001) and 12 weeks (p < 0.001) (see figure 6a), while in the evening evaluations a significant improvement were detected at 2 (p < 0.001), 4 (p < 0.001) and 12 weeks (p < 0.001) (see figure 6b).

Finally, the change in score from baseline after the first 12 h was also evaluated, showing runny nose, itchy nose and sneezing as significantly (p < 0.001) better than placebo.

The total AEs incidences was 25% (n=126) for patients taking placebo and 38% (n=194) and for rupatadine 10 mg (p < 0.01). Both groups of treatment showed a similar pattern of safety, including some side effects in gastrointestinal and SNC systems. Only the incidence of somnolence was statistically significant with rupatadine in comparison with placebo (p < 0.01).

### 4 Discussion

The second generation of anti-H₁ antihistamines play an important role in the treatment of AR at all severity stages, and are indeed recommended by current guidelines (Bousquet et al., 2008).
Figure 4: Itching nose. (a) Morning: AM evaluation; (b) Evening: PM evaluation. Mean change from baseline over 2, 4, 8 and 12 weeks.

Figure 4: Blocked nose. (a) Morning: AM evaluation; (b) Evening: PM evaluation. Mean change from baseline over 2, 4, 8 and 12 weeks.

Figure 6: Sneezing. (a) Morning: AM evaluation; (b) Evening: PM evaluation. Mean change from baseline over 2, 4, 8 and 12 weeks.
The symptoms of AR vary in severity over the course of the day and are often worse in the morning. Actually, the intensity of nasal congestion, rhinorrhea and sneezing are greater early in the morning in approximately 70 % of patients (Schenkel, 2006; Smolensky et al., 1995). This is true for patients with seasonal symptoms alone (55.9%) and also for those with PAR (65.7%), although it is noteworthy that those with PAR reported worse symptoms in the morning significantly more often than those with SAR (Binder et al., 1982). Therefore, in order to maximize the benefits for patients and also to maintain a good overall efficacy profile, any pharmacologic agent used in the management of allergic rhinitis should be effective in controlling these peak morning symptoms. In general, antihistamines would be expected to exert their maximum effect near or shortly after peak serum levels are reached. In the case of rupatadine, previous studies showed a fast on-set of action (Mullol et al. 2008), due to the fact that levels reach its peak serum levels around 0.5 – 1 hour after dosing (Keam et al., 2007). This was the main reason why morning dosages scheduled in our study and so we expected to observe a greater relief of morning symptoms in comparison with those evening symptoms. Notably, in our study, the overall (T4SS) relief of symptoms was quite similar for AM or PM period with rupatadine 10 mg once daily, indicating a sustained 24-hour effect of rupatadine irrespective of time of dosing. These 4TSS values are in concordance with previous clinical controlled studies of rupatadine using active controls (Fantin et al., 2008; Lukat et al., 2013).

When individual nasal symptoms were evaluated at AM or PM, different patterns were observed. The morning evaluations showed all symptoms’ scores well controlled, with a high significant improvement in all treatment periods (from 2 to 12 weeks). Specifically, a significant capacity to alleviate sneezing and nasal blockage in the morning was provided by rupatadine in all evaluated periods. Nasal congestion is a particularly troublesome symptom of allergic rhinitis and is often cited by patients as the most bothersome one. Newer antihistamines have demonstrated anti-inflammatory properties which could play a role in the control of nasal inflammation. However the results of their effects clinical trials on nasal congestion are not enough conclusive (Horak, 2002). Rupatadine was previously shown to reduce nasal congestion effectively in patients with SAR, having been measured, both objectively in terms of nasal airflow or subjectively in terms of symptoms in allergen exposure study (Stübner et al., 2006; Valero et al., 2009).

The nighttime symptoms are an important component of the total morbidity associated with AR. Both sleep disorders and AR are associated with increases in daytime somnolence, fatigue, irritability, absenteeism and performance impairment. It is clear that nasal itching and runny nose do not improve sleep quality; however, nasal congestion is thought to be the main symptom responsible for rhinitis-related sleep problems (Juniper et al., 2003).

In our analysis of the nighttime symptoms, runny nose and itchy nose were not well controlled, and actually they did not achieve statistically significant improvements in comparison with placebo. These findings may be explained in part by the fact that these symptoms were most likely underreported (by the patients) in the clinical trials. Additionally, it seems that there was not enough statistical power to found significant differences between both group’s scores. Sneezing and nasal blockage are symptoms which may be particularly troublesome for patients at nighttime. Sneezing could delay the onset of sleep and nasal blockage, subsequent to nasal congestion, can lead to pathologic changes in airflow velocity and increase the sleep-disordered breathing (Young et al., 1998). In our pooled analysis rupatadine reduce the sneezing and nasal blockage at nighttime e in comparison with placebo.

In relation with the incidence of side effects, was low and most of them have been previously reported with antiH1 second generation, like gastrointestinal and central nervous system side effects. Mild
somnolence episodes were more frequent related with rupatadine treatment. There was a consistent low frequency of somnolence across the studies in those patients receiving rupatadine (Fantin et al., 2011; Guadaño et al., 2004; Izquierdo et al., 2000; Lukat et al., 2013; Marmouz et al., 2011).

The specific underlying mechanisms of the chronobiology of AR are not clear established; however, several factors might contribute to the occurrence of maximum nasal blockage, sneezing and rhinorrhea in the morning: secretions increase and accumulate overnight; there is continuous allergen exposure to mold, mites or house dander; cortisol levels are lowest at night, and hence inflammatory mediators might be at high levels; and autonomic nervous system activity at night promotes vagal tone, favoring vasodilation (Meltzer, 2002).

In this analysis, rupatadine maintains its effect throughout the day and at different periods of treatment duration (from 2 to 12 weeks) and apparently shows no circadian variation of effect when the symptoms are globally evaluated. This activity could be explained by an additional and sustained anti-inflammatory effect of rupatadine (Mullol et al., 2008). These patients have a continuous inflammation in the nose caused by the persistent allergen exposure throughout the years. This concept of a minimal persistent inflammation would involve, at least in theory, several mediators produced by primary effector cells, which would play an important role in the onset and maintenance of the inflammatory allergic process (Ciprandi et al., 1995). As a consequence, active drugs like rupatadine, capable of interfering with more than one class of these mediators, could provide a better control for allergic inflammatory symptoms in comparison with other anti-H1 compounds which have not this simultaneous blocking capacity (Fantin et al., 2008).

In conclusion, the sustained 24-hour action of rupatadine 10 mg provides an effective control of morning and evening symptoms from 2 up to 12-weeks of treatment in patients with several subtypes of allergic rhinitis.

**Competing interests**

The study was funded by J Uriach y Compañia, S.A (Barcelona, Spain). The authors are employees of Clinical development Dept at J Uriach Company.

**Author’s contributions**

II participated in the design of study, analysis interpretation and drafting of the manuscript. JG participated in the statistical analysis, the tables and figures preparation and drafting the manuscript. AD participated in the analysis interpretation and reviewing the manuscript.

**References**


