ORIGINAL ARTICLE

Reduction of Nasal Volume After Allergen-Induced Rhinitis in Patients Treated With Rupatadine: A Randomized, Cross-Over, Double-Blind, Placebo-Controlled Study

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Abstract

Objective: To measure the reduction in nasal obstruction using acoustic rhinometry in patients with allergic rhinitis treated with rupatadine.
Methods: We performed a randomized, double-blind, cross-over, placebo-controlled clinical trial in asymptomatic patients with allergic rhinitis. Patients received rupatadine 10 mg or placebo once daily for 3 days, in 2 subsequent periods separated by a washout interval of 14 days. We performed a nasal allergen challenge during each period, and measured nasal volume using acoustic rhinometry and nasal nitric oxide (nNO) at baseline, and at 2 hours and 24 hours after the challenge. We also evaluated nasal symptoms (rhinorrhea, itching, obstruction, and sneezing), as well as total symptom score (T4SS) at the same time points as for the primary objective.
Results: The study population comprised 30 outpatients with a mean (SD) age of 28 (10) years. Nasal airway blockage was significantly lower in the rupatadine group than in the placebo group (47%, $P<.05$) at 2 hours postchallenge. nNO in the rupatadine-treated patients remained unaltered, unlike in the placebo-treated group, where levels decreased at 2 hours. After treatment with rupatadine, patients showed a lower decrease in the mean total symptoms score at 2 hours (3.6 [2.6]) compared with placebo (3.9 [2.9]), although these differences did not achieve statistical significance. Overall, rupatadine was well tolerated and no serious or unexpected adverse events were observed.
Conclusions: Rupatadine 10 mg can reduce nasal obstruction assessed by objective measures and is well tolerated in patients with allergic rhinitis.

Key words: Acoustic rhinometry. Nasal obstruction. Nasal allergen challenge. Rupatadine.

Resumen

Objetivo: El objetivo de este estudio fue evaluar la reducción de la obstrucción nasal medida por rinometría acústica (RA) en pacientes con rinitis alérgica y tratados con rupatadina.
Métodos: Diseñamos un estudio a doble ciego, cruzado, aleatorizado y controlado con placebo en pacientes asintomáticos con rinitis alérgica. Los pacientes fueron tratados con rupatadina 10 mg o placebo una vez al día durante los 3 días previos, en dos subsecuentes periodos separados por un periodo de blanqueo de 14 días. En cada periodo fue realizada una provocación nasal con alergeno, midiéndose el volumen nasal por RA y la liberación del oxido nítrico nasal (ONn) a los tiempos basal, 2 y 24h después de la provocación. Los síntomas nasales incluyendo, rinorrea, prurito, obstrucción, estornudos y la suma global de síntomas (T4SS) fueron también evaluados a los mismos tiempos que los objetivos primarios.

vías áreas nasales obtenido por RA tras el test de provocación alergénica fue observado en el grupo de rupatadina en comparación con el grupo placebo (47%, *P*<0.05) a las 2 horas post-provocación. Los valores de ONn con el grupo de pacientes tratados con rupatadina fue similar al observado en condiciones basales, al contrario que en el grupo placebo, donde se observó que dichos niveles eran inferiores a las 2 h. Después del tratamiento con rupatadina los pacientes mostraron una disminución del puntaje total de síntomas (4TSS) a las dos horas (media: 3.6 ± 2.6) comparado con el placebo (3.9±2.9), no obstante estas diferencias no fueron estadísticamente significativas.En general, rupatadina fue bien tolerada y no se reportaron efectos adversos graves o inesperados al tratamiento.
Conclusión: Rupatadine 10 mg es efectiva en la reducción de la obstrucción nasal valorada mediante medidas objetivas y además presentó una buena tolerancia en los pacientes con rinitis alérgica..

Palabras clave: Rinometría acústica. Obstrucción nasal. Provocación nasal alergénica. Rupatadina.

Introduction

Nasal obstruction is a severe symptom in patients with allergic rhinitis [1] and is the most bothersome manifestation of chronic allergic inflammation; therefore, the anti-inflammatory properties of an H_1 antihistamine must be quantifiable. This is all the more necessary in persistent allergic rhinitis, in which obstruction predominates over the other histamine-induced symptoms.

Acoustic rhinometry is used to assess the geometry of the nasal cavities, including both the cross-sectional areas and the volume of the nasal cavities at various distances from the nostrils. This reliable and objective technique enables us to assess nasal airway obstruction after a nasal allergen challenge in allergic patients [2].

Nitric oxide (NO) mediates various biological processes, including vasodilatation and cellular immune response. Its metabolites are found in high concentrations in the nose of both healthy individuals and patients with rhinitis [3]. This is attributed to the high levels of NO in the paranasal cavities, from which it flows toward the nasal cavity. Considering changes in this mediator as an indicator of inflammation could help us evaluate the effectiveness of treatment [4].

Rupatadine is a new once-daily nonsedating H_1 antihistamine and platelet activating factor antagonist [5-6]. This combined effect may provide a special advantage in the current treatment of patients with seasonal and perennial allergic rhinitis [7-8], and the drug has recently been administered in persistent allergic rhinitis [9].

Our main objective was to evaluate the reduction in delayed nasal obstruction as measured by acoustic rhinometry in patients treated with rupatadine after a nasal allergen challenge, and to determine nasal NO (nNO) values in a group of asymptomatic allergic patients.

Patients and Methods

Patients and Study Design

To be eligible for the study, patients had to be asymptomatic and aged between 18 and 60 years. They also had to have had a more than 2-year history of persistent or intermittent pollen-induced allergic rhinitis according to the guidelines of the ARIA-Allergic Rhinitis and Its Impact on Asthma group [10]. A randomized, cross-over, double-blind, placebo-controlled clinical trial was performed to evaluate the effect of rupatadine on nasal obstruction (Figure 1)

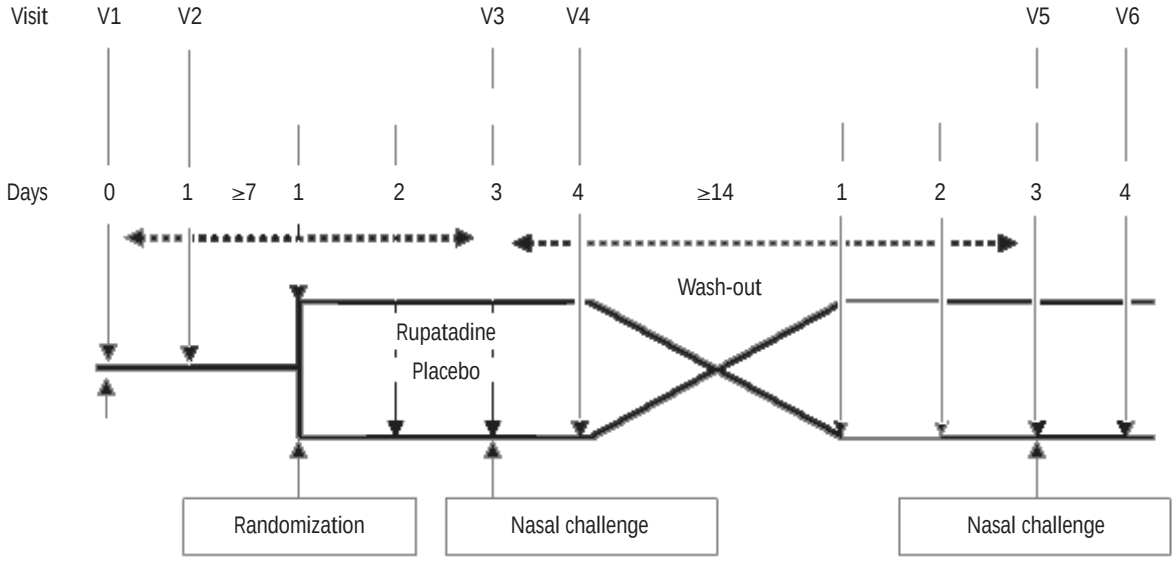

Figure 1. Study design. Flow diagram showing calendar of visits, nasal challenge performed, and sequence of treatment periods.

The study patients had not received any of the following: depot corticosteroids in the 2 months before inclusion; topical, inhaled or systemic corticosteroids in the 2 weeks before inclusion; or antihistamines or antileukotrienes during the week before inclusion. Furthermore, a nasal provocation test was conducted during the screening period to verify eligibility and set the allergen concentration to be used with each participant. Patients were instructed to self-administer rupatadine 10 mg or placebo once daily in the morning for 3 days, in 2 subsequent periods separated by a washout interval of 14 days. Nasal blockage was evaluated by acoustic rhinometry and nasal and exhaled NO at baseline, 2 hours, and 24 hours after the provocation test.

All the patients understood and met with the requirements of the study and provided written informed consent before enrolment. The study was approved by the Ethics Committee of our hospital and the Spanish Medications Agency.

Acoustic Rhinometry

Nasal volume was measured using acoustic rhinometry (SER 2000 RhinoMetrics, Lynge, Denmark) during screening, at baseline, and at 2 hours and 24 hours after the allergen challenge. During screening, an additional measurement was taken 15 minutes after the challenge in order to set the threshold allergen dose.

Because the main changes in nasal geometry occur in the most vascularized segment, the nasal volume was evaluated between the second and fifth centimeters (Vol_{2-5}) of the nasal cavity using a standardized method [2].

Determination of nNO Values

nNO was measured after acoustic rhinometry at the same time points using a chemiluminescence-based technique (SIR System N6008 NO tracer, SIR, Madrid, Spain) following a standardized method [11].

Nasal Provocation Test

The nasal provocation test was performed using solutions containing extracts of the relevant clinical allergens (Diater, Madrid, Spain)—grass (21 cases), Parietaria (3 cases), olive (3 cases), and plane tree (3 cases)—in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology [12].

During screening, a baseline measurement of nasal volume was taken (Vol_{2-5}) using acoustic rhinometry, and a control solution was applied to the nostril. Fifteen minutes later, if no reaction was detected by acoustic rhinometry, the solution with the relevant allergen was applied. Allergen doses were increased (1/100, 1/10, and 1/1) until the threshold dose was reached. This was defined as the allergen dose that enabled a decrease in nasal volume ≥30% of the volume after the control provocation for each patient. This threshold allergen dose was used to induce nasal blockage in the provocation tests.

Assessment of Symptoms

Nasal symptoms, including rhinorrhea, itching, obstruction, and sneezing, as well as the total symptom score were also evaluated, at the same time points as the primary objective measurements using a severity score with a conventional categorical scale (0, none; 1, mild; 2, moderate; 3, severe; 4, very severe).

Safety and Tolerability

The safety and general tolerability of the treatments were based on adverse events recorded during the study.

Statistical Analysis

For quantitative variables, the mean, median, standard deviation, maximum and minimum were calculated. Qualitative variables were expressed as relative frequencies.

Descriptive analyses were used to summarize demographic data, baseline characteristics, and postbaseline efficacy measurements.

The results of the screening evaluations of the efficacy variables were analyzed using the nonparametric Wilcoxon signed-rank test.

Analysis of covariance (ANCOVA) was used to compare the mean change from baseline between the treatment groups. The effects of sequence and period were taken into account. To decrease the variability of the data, the efficacy variables were transformed using the logarithmic function.

All statistical tests were performed using SAS version 8.2 for Windows (SAS Institute Inc, Cary, North Carolina, USA). *P* values less than .05 were considered statistically significant.

Results

The 30 patients enrolled (9 men) were all Caucasian, with a mean (SD) age of 28 (10) years and allergic rhinitis in the asymptomatic phase. The main demographic and baseline characteristics of the patients are summarized in Table 1.

All the patients completed the screening battery. When the screening challenge procedure was performed, 43% of the participants achieved the established 30% decrease in nasal volume 15 minutes after the provocation with a concentration of 1/100 of the sensitized allergen, 37% achieved it with a concentration of 1/10, and 20% with a concentration of 1/1. Screening values at baseline and after the nasal challenge provocation are shown in Table 2.

Table 1. Demographic Characteristics of Patients at Baseline[a]

	Treatment Group (N=30)
Men/Women	9/21
Age, y	27.6 (10.1)
Nasal volume (Vol_{2-6}), cm^3	5.64 (2.2)
Nasal nitric oxide, ppb	1497 (765)
Exhaled nitric oxide, ppb	15.8 (20.2)
FEV_1, %	95 (7.1)
Total nasal symptom score	1.5 (1.7)

Abbreviation: FEV_1, forced expiratory volume in 1 second.
[a] Data are expressed as mean (SD).

Table 2. Screening Values at Baseline and After the Nasal Challenge Provocation[a]

	Mean Change From Baseline at 15 Minutes		Mean Change From Baseline at 2 Hours		Mean Change From Baseline at 24 Hours	
Nasal volume (Vol_{2-5}), cm^3	–2.5 (0.3)	*P*<.001	–0.6 (0.3)	*P*=.02	–0.3 (0.5)	NS
Nasal nitric oxide, ppb	–547 (114)	*P*<.001	–269 (74)	*P*<.001	–53 (111)	NS

Abbreviation: NS, nonsignificant.
[a] Data are expressed as mean (SD).

Table 3. Absolute Values for Nasal Volume (Vol_{2-5}) and Nasal Nitric Oxide by Treatment Group[a]

	Placebo			Rupatadine		
	Baseline	2 hours	24 hours	Baseline	2 hours	24 hours
Nasal volume (Vol_{2-5}), cm^3	5.54 (0.39)	4.42 (0.33)	5.27 (0.38)	5.54 (0.46)	4.77 (0.40)	5.21 (0.44)
Nasal nitric oxide, ppb	1455.92 (147.59)	1192.38 (156.56)	1421.74 (161.87)	1445.00 (147.77)	1483.80 (141.18)	1416.35 (182.71)

[a] Data are expressed as mean (SD).

Table 4. Mean Change From Baseline in Nasal Volume (Vol_{2-5}) and Nasal Nitric Oxide by Treatment Group[a]

	Mean Change From Baseline at 2 Hours			Mean Change From Baseline at 24 Hours		
	Rupatadine	Placebo	*P* Value	Rupatadine	Placebo	*P* Value
Nasal volume (Vol_{2-5}), cm^3	-0.78 (0.20)	-1.12 (0.18)	*P*=.02	-0.34 (0.27)	-0.34 (0.22)	NS
Nasal nitric oxide, ppb	86 (82)	-288 (126)	NS	27 (107)	-22 (72)	NS

Abbreviation: NS, nonsignificant.
[a] Data are expressed as mean (SD).

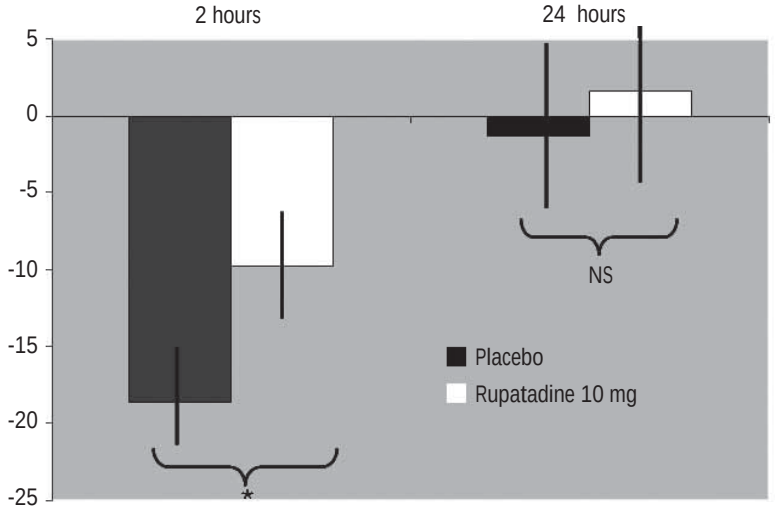

Figure 2. Percentage change in nasal volume (Vol_{2-5}) by acoustic rhinometry at 2 hours and 24 hours following allergen challenge in the placebo and rupatadine groups. NS indicates not significant.
[a]*P*<.05.

The nasal challenge revealed nonsignificant differences between the volumes measured at baseline and after administration of the saline solution (5.64 cm^3 vs 5.63 cm^3, *P*=.172). Two hours after the nasal challenge, a significantly lower nasal airway caliber was observed in the rupatadine group (47%, *P*<.05). Nasal volume diminished 9.8% in patients previously treated with rupatadine compared with 18.6% in those treated with placebo 2 hours after the challenge. Nasal volume returned to baseline values 24 hours after the challenge in both groups (Tables 3 and 4) (Figure 2).

nNO was maintained with respect to baseline in the rupatadine group (1445 [723] ppb vs 1483 [706] ppb), but not in the placebo group (*P*=.056), where it was observed that levels were decreased at 2 hours (1456 [723] ppb vs 1192 [717] ppb) but reached baseline values again at 24 hours (Table 3 and 4).

The patients were practically asymptomatic before the end of the 2 nasal challenges. After treatment with rupatadine, patients showed a lower reduction in mean total symptom score at 2 hours (3.6 [2.6]) compared with placebo (3.9 [2.9]), although this difference did not achieve statistical significance. A trend toward relief was observed in each of the nasal symptoms evaluated (rhinorrhea, itching, obstruction, and sneezing). Most of the patients in both groups reached their baseline values at 24 hours after challenge.

Rupatadine was well tolerated, and nonsevere or unexpected adverse events were reported.

Discussion

We observed a significantly greater decrease (*P*<.05) in nasal airway caliber following allergen challenge in the placebo group than in the rupatadine group (47%) 2 hours after challenge. No differences were detected 24 hours after challenge.

Nasal obstruction is an important symptom in patients with allergic rhinitis [1], and previous studies with rupatadine have shown a significant reduction in nasal obstruction in this group [13]. Similar benefits were reported by Stuebner et al [14] in a group of 45 patients with seasonal allergic rhinitis pretreated with rupatadine 10 mg or placebo undergoing 6-hour allergen exposure in a Vienna Challenge Chamber. Rupatadine was more effective at relieving nasal and ocular symptoms (including nasal congestion) than placebo. We evaluated reduction of nasal blockage using acoustic rhinitis, which is considered an objective method in the assessment of nasal patency.

nNO in the controls decreased compared with baseline, unlike the rupatadine group, in which these levels were maintained. This could be due to a less intense inflammation of nasal turbinates that allows NO to flow from the sinus into the nasal cavity, whereas the higher obstruction in the placebo group most probably blocked the sinus and impaired sinus NO diffusion [4].

Two previous nasal provocation studies have evaluated the nNO response. Kharitonov et al [15] studied 5 patients with seasonal allergic rhinitis outside the pollen season. One hour after the start of the challenge, when symptoms were at a peak, there was a maximal decrease in nNO concentrations, which returned to baseline values 4 hours after challenge. In the study by Maniscalco et al [16], 9 patients underwent challenge with seasonal allergy outside the pollen season, and nNO levels remained unaltered. The difference in the effect of the challenge on nNO concentration might depend on the concentration of allergen extract administered. In Kharitonov's study, it can be assumed that administering a high dose of grass-pollen extract at once will induce a potent reaction leading to blockage of the sinuses due to mucosal swelling and thus influencing nNO compared with administration of a lower total allergen dose in several steps (Maniscalco). A paradoxical low nNO has also been reported in patients with nasal polyposis, suggesting that the intense inflammation usually present in nasal polyposis results in obstruction of the ostiomeatal complex, which in turn reduces the diffusion of NO from the paranasal sinus to the nasal cavity [4,17].

We also observed a mild improvement in nasal symptoms 2 hours after challenge; this correlates with the objective improvement in nasal volume observed by acoustic rhinometry. However, the change in nasal symptoms did not reach statistical significance, probably due to the low number of patients in this subjective evaluation.

In summary, rupatadine 10 mg once daily for 3 days is effective at reducing nasal obstruction following allergen challenge, as assessed using objective measures (acoustic rhinometry).

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