ORIGINAL ARTICLE

Comparative Effect of Beclomethasone Dipropionate and Cetirizine on Acoustic Rhinometry Parameters in Children With Perennial Allergic Rhinitis: A Randomized Controlled Trial

Malizia V[1], Fasola S[1,2], Ferrante G[3], Cilluffo G[1,2], Gagliardo R[1], Landi M[1,4], Montalbano L[1,5], Marchese D[1], La Grutta S[1,3]

[1]National Research Council of Italy, Institute of Biomedicine and Molecular Immunology, Palermo, Italy
[2]Department of Economics, Business and Statistical Science, University of Palermo, Italy
[3]Department of Science for Health Promotion and Mother and Child Care, University of Palermo, Italy
[4]National Healthcare System, ASL TO3, Turin, Italy
[5]Department of Psychology, University of Palermo, Italy

J Investig Allergol Clin Immunol 2018; Vol. 28(6): 392-400
doi: 10.18176/jiaci.0263

Abstract

Background: The effect of intranasal corticosteroids and oral antihistamines on acoustic rhinometry parameters has not been directly compared.
Objectives: The primary objective was to compare the effect of a 21-day course of treatment with nasal beclomethasone dipropionate (nBDP) with that of cetirizine (CTZ) on nasal patency measured using acoustic rhinometry in children with perennial allergic rhinitis (PAR). The secondary objective was to compare the effect of both drugs on nasal cytology, symptom severity, sleep quality, and quality of life.
Methods: In this 21-day, open-label, randomized controlled study, 34 children with PAR (age 6-14 years) with a Total 5-Symptom Score (T5SS) ≥5 received nBDP 100 µg per nostril twice daily or CTZ 10 mg tablets once daily. The measures of effect were the least square mean change (LSmc) in nasal volume, minimal cross-sectional area (MCA), and nasal cytology, as well as the scores on the T5SS, Pittsburgh Sleep Quality Index (PSQI), and Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).
Results: After 21 days, nBDP improved nasal volume and MCA more than CTZ (LSmc, 2.21 cm^3 vs 0.20 cm^3 [*P*=.013]; and LSmc 0.63 cm^2 vs 0.13 cm^2 [*P*=.002], respectively). Compared with the CTZ group, a more marked improvement was found in the nBDP group with respect to eosinophil classes (LSmc, –1.10 vs –0.40; *P*=.031) and neutrophil classes (LSmc, –0.97 vs –0.17; *P*=.010), T5SS (LSmc, –5.63 vs –3.54; *P*=.008), PSQI (LSmc, –1.30 vs –0.19; *P*=.025), and PRQLQ total scores (LSmc, –1.15 vs –0.69; *P*=.031).
Conclusions: In children with PAR, nBDP is more effective than CTZ in improving nasal patency measured by acoustic rhinometry, with associated beneficial effects on nasal cytology, symptoms, sleep quality, and quality of life.

Key words: Acoustic rhinometry. Allergic rhinitis. Beclomethasone dipropionate. Cetirizine. Children. Nasal patency.

Resumen

Antecedentes: No hay estudios previos en los que se comparan los efectos sobre la rinometría acústica de los corticoides intranasales y los antihistamínicos orales.
Objetivos: El objetivo principal fue comparar los efectos de un tratamiento de 21 días con dipropionato de beclometasona (nBDP) frente a ceterizina (CTZ) sobre la obstrucción nasal medida con rinometría acústica en niños con rinitis alérgica perenne (PAR). Los objetivos secundarios incluyen los efectos sobre la citología nasal, la gravedad de los síntomas, la calidad del sueño y la calidad de vida.
Métodos: Estudio abierto, aleatorizado y controlado, de 21 días de duración. Se incluyeron 34 niños con PAR (6-14 años) con una puntuación de síntomas ≥5 (T5SS) que recibieron 100 µg de nBDP por fosa nasal dos veces al día o CTZ 10 mg una vez al día. Se realizaron las siguientes mediciones: cambios en los mínimos cuadrados (LSmc) del volumen nasal, del área transversa mínima (MCA), de la citología nasal, el T5SS, índice de calidad del sueño (PSQI) y el cuestionario de calidad de vida pediátrico (PRQLQ).
Resultados: después de 21 días, los tratados con nBDP mejoraron el volumen nasal y el MCA más que los tratados con CTZ (LSmc 2,21 cm^3 *vs* 0.20 cm^3, p=0,013 and LSmc 0,63 cm^2 *vs* 0,13 cm^2, p=0,002, respectivamente). En el grupo tratado con nBDP, con respecto a los tratados con CTZ tuvieron una mayor mejoría en la disminución de clases de eosinófilos (LSmc -1,10 vs -0,40, p=0,031) y neutrófilos (LSmc -0,97 vs -0,17, p=0,010), en el T5SS (LSmc -5,63 vs -3,54, p=0,008), PSQI (LSmc -1,30 vs -0,19, p=0,025) y en la puntuación total de PRQLQ (LSmc -1,15 vs -0,69, p=0,031).

Conclusiones: en niños con PAR, la nBDP es más efectiva que la CTZ en mejorar la obstrucción nasal medida por rinometría acústica, con los beneficios asociados sobre citología nasal, síntomas, calidad de sueño y calidad de vida.

Key words: Rinometría acústica. Rinitis alérgica. Dipropionato de beclometasona. Ceterizina. Niños. Obstrucción nasal.

Introduction

Allergic rhinitis is the most common form of rhinitis in childhood. It is characterized by at least 2 symptoms from among nasal itching, sneezing, rhinorrhea, and nasal congestion [1]. In particular, nasal congestion, defined as the discomfort experienced during breathing due to decreased nasal patency, is recognized as one of the most bothersome symptoms [2,3].

Nasal patency can be evaluated subjectively using symptom severity scales [4-6] or objectively using clinical measures [7], such as acoustic rhinometry, a validated noninvasive tool applied to measure the area and volume of the nasal cavity [8]. In children, measurement of volume in the anterior part of the nose has been shown to be sensitive for changes in nasal patency due to changes in mucosal swelling after the nasal provocation test [9] and after decongestion [10]. Nasal cytology can also be used for objective evaluation of mucosal inflammation and provides insights into the efficacy of therapeutic interventions [11,12].

There is strong evidence for the efficacy of intranasal corticosteroids (INCs) in patients with perennial allergic rhinitis (PAR) [13]. Nasal beclomethasone dipropionate (nBDP), in particular, has been shown to be effective both in reducing eosinophils and lymphocytes in the nasal mucosa and in relieving nasal symptoms [14]. Oral antihistamines are also recommended [13], and cetirizine (CTZ) has proven effective in relieving symptoms [15].

Previous clinical studies in children with PAR demonstrated the efficacy of INCs and oral antihistamines in improving acoustic rhinometry parameters and other subjective outcomes [16,17]. However, these outcomes were evaluated only through independent intragroup analyses or comparisons with placebo, and no studies directly compared both active treatments. Moreover, previous studies used different methodologies and therapeutic interventions, with the result that objective and subjective outcomes have not been comprehensively evaluated.

The primary aim of the present study was to compare the effect of nBDP with that of CTZ on nasal patency measured using acoustic rhinometry in children with PAR. The secondary aim was to compare the effect of nBDP and CTZ on other objective parameters (nasal cytology) and subjective parameters (nasal symptom severity, sleep quality, quality of life).

Materials and Methods

Study Design

This single-center, open-label, randomized controlled study was approved by the local Institutional Ethics Committee (Palermo 1, Italy, Approval Number: 09/2015), and informed consent was obtained from all parents before study entry. Once approved, the study was registered on ClinicalTrials.gov (ID: NCT02646904). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Participants

The initial study population comprised 128 children with PAR. The children were aged 6-14 years and had been assessed for eligibility at the pediatric allergy outpatient clinic of the Institute of Biomedicine and Molecular Immunology, National Research Council of Italy, Palermo, Italy between May 2016 and July 2017. The inclusion criteria were as follows: (*1*) age 6-14 years; (*2*) clinical history of PAR in the previous year, according to ARIA guidelines [18]; (*3*) allergic sensitization to *Dermatophagoides pteronyssinus*, defined as a positive skin prick test response (wheal ≥3 mm larger than the negative control test [Stallergenes]) after 15 minutes [19]; (*4*) Total 5-Symptom Score (T5SS) ≥5 (rhinorrhea, nasal obstruction, nasal itching, sneezing, eye itching) [4] in the previous week. The exclusion criteria were as follows: (*1*) positive skin prick test result to seasonal allergens and other perennial allergens; (*2*) medical diagnosis of nasal anatomic defects (ie, deviated septum) or nasal polyp disease; (*3*) medical diagnosis of asthma according to GINA guidelines (http://ginasthma.org); (*4*) upper or lower respiratory tract infection in the previous 2 weeks; (*5*) use of oral antihistamines, decongestants, leukotriene antagonists, systemic/topical antibiotics or corticosteroids in the previous 4 weeks; (*6*) ongoing allergen immunotherapy; (*7*) active smoking; (*8*) adherence <80%.

Interventions

According to a computer-generated randomization sequence (1:1 allocation) that was unknown to the physicians, the 68 eligible patients were assigned to one of two 21-day treatments: 34 children received nBDP 100 µg per nostril twice daily (beclomethasone dipropionate nasal spray suspension); 34 children received CTZ 10 mg once daily (oral tablets, 10 mg). Both nBDP and CTZ were provided by CHIESI Farmaceutici S.p.A. All patients and their caregivers were given a brief demonstration of how to use the nasal spray suspension.

Outcomes

The primary outcome was the change from baseline to 21 days of treatment in acoustic rhinometry parameters, namely, nasal volume and minimal cross-sectional area (MCA). Acoustic rhinometry was carried out using the A1 Acoustic Rhinometer (GM Instruments) and the accompanying software according to the manufacturer's instructions. All measurements were performed by the same pediatrician (VM). The device was calibrated prior to each measurement. Following current recommendations, patients were tested after 20 minutes of acclimatization in the test room [20]. Special soft nosepieces for children were used. If necessary, ultrasound gel was used to prevent acoustic leakage. No nasal decongestant was used. Calculations were based on the mean values of 3 acceptable measurements with a standard deviation of less than 5%. The values of special interest were the nasal volume (cm^3) in the first 5 cm from the nostril and the MCA (cm^2). Total values were calculated by adding each nostril value.

The secondary outcomes were the changes from baseline to 21 days of treatment in nasal cytology classes and in a series of subjective scales (see below).

Nasal cytology was performed using a small plastic curette (Rhinoprobe) in anterior rhinoscopy, following recent recommendations [21]. Neutrophils and eosinophils were classified as follows: 0, none; 1, few scattered cells; 2, moderate number; 3, large clusters [21].

The T5SS is a subjective scoring system for determination of symptom severity based on 5 domains: rhinorrhea, nasal obstruction, nasal itching, sneezing, and eye itching. Each symptom is scored on a 4-point scale from 0 to 3. The total score is calculated by adding the scores for all 5 domains and ranges from 0 (nonsevere) to 15 (extremely severe) [4].

The Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire based on 4-week recall and including 19 questions in 7 domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Each domain is scored from 0 to 3, so that the total score ranges from 0 (good sleeper) to 21 (poor sleeper) [22].

The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is a self-administered questionnaire based on 4-week recall for assessing physical, emotional, and social problems in persons with allergic rhinitis. It includes 23 items in 5 domains: nose symptoms, eye symptoms, practical problems, activity limitation, and other symptoms. Each domain is scored on a 7-point scale (from 0 [good quality] to 6 [poor quality]). The overall score is obtained from the mean score of all the items [23].

Assessments

A detailed medical history was obtained by well-trained physicians (VM, GF, SLG) to investigate clinical symptoms, host factors, and environmental exposures. In particular, information about current exposure (previous 12 months) to passive smoke, mold, pet dander, and traffic was derived from a standardized questionnaire administered to parents [24].

The study involved 3 visits: screening (visit 1), randomization (visit 2, baseline), and final assessment (visit 3, day 21+1). At visit 1, patients were assessed for eligibility and recruited if they met the inclusion criteria. Typically, 1 to 7 days elapsed from enrolment to randomization. Patients underwent a physical examination, and study variables were assessed at each visit. When necessary, questionnaires were completed under the supervision of one of the researchers (LM) during the visits.

Patients and caregivers were instructed to record the occurrence and severity of adverse effects on a diary card throughout the treatment period. They also recorded information about the severity of nasal symptoms, use of concomitant medications, and adherence. Good adherence was defined as completion of ≥80% of the scheduled treatment.

Sample Size

The sample size was based on pilot data from a previous study [17] investigating the effect of topical nasal corticosteroids on nasal volume in children and adolescents with PAR. In the aforementioned study, the nasal volume increased from a baseline mean value of 8.2 cm^3 to 9.3 cm^3 (SD approximately 1.5). Detecting a similar change with an 80% statistical power and a 5% significance level would have required a sample size of 30 children for each treatment group. To account for a hypothesized dropout rate of 10% to 15%, the sample size was established at 34 patients per group.

Statistical Analysis

The baseline characteristics of the children were compared between the nBDP and CTZ groups using the *t* test for 2 means (quantitative variables) and the χ^2 test for percentages (categorical variables). Correlations between acoustic rhinometry parameters and other objective and subjective scores were evaluated using the Kendall τ test.

The treatment effect was assessed in children who completed the study. For the primary outcomes, an exploratory analysis was performed using the Wilcoxon test to assess the change from baseline in the 2 treatment groups. For both the primary and secondary outcome measures, the mean change from baseline in the 2 treatment groups was compared using linear regression models adjusted for age, weight, current exposure to smoke, mold, dander (cat and/or dog), traffic

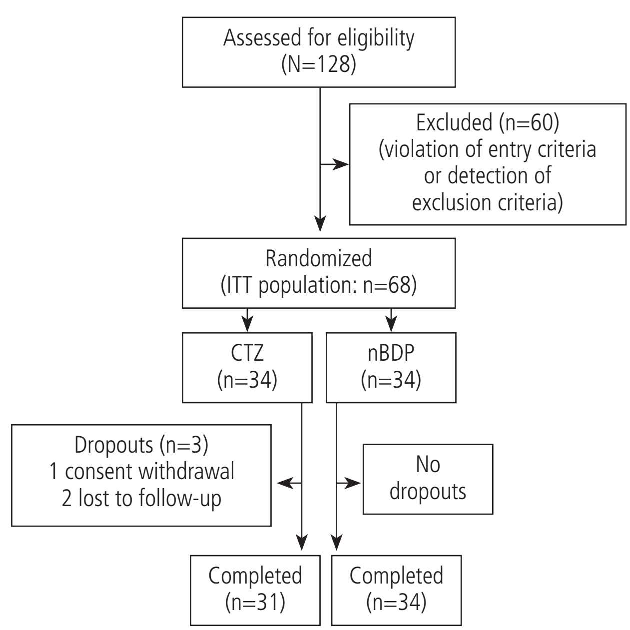

Figure 1. Study flowchart. ITT indicates intention-to-treat; CTZ, cetirizine; nBDP, nasal beclomethasone dipropionate.

doi: 10.18176/jiaci.0263

Table 1. Characteristics of Children at Baseline[a]

	CTZ (n=34)	nBDP (n=34)	*P* Value[a]
Anthropometric characteristics			
Gender			.800
Male	23 (68%)	21 (62%)	
Female	11 (32%)	13 (38%)	
Mean (SD) age, y	9.47 (2.36)	10.06 (2.35)	.307
Mean (SD) weight, kg	36.94 (11.2)	37.56 (14.03)	.842
Mean (SD) height, cm	139 (14.47)	139.59 (16.37)	.877
AR duration, y			.487
1-3	16 (47%)	14 (41%)	
4-5	5 (15%)	9 (28%)	
>5	13 (38%)	11 (31%)	
Current environmental exposures[b]			
Passive smoke	8 (24%)	8 (24%)	1.000
Mold	8 (24%)	5 (15%)	.537
Dog	9 (26%)	6 (18%)	.559
Cat	3 (9%)	3 (9%)	1.000
Traffic density			.576
Absent	4 (12%)	6 (18%)	
Low	10 (29%)	13 (38%)	
Moderate	7 (21%)	7 (21%)	
High	13 (38%)	8 (24%)	

Abbreviations: AR, allergic rhinitis; CTZ, cetirizine; nBDP, nasal beclomethasone dipropionate.
[a]*t* test for quantitative variables, χ^2 test for categorical variables.
[b]Previous 12 months.

Table 2. Primary and Secondary Outcomes at Baseline[a]

	CTZ (n=34)	nBDP (n=34)	*P* Value[b]
Acoustic rhinometry			
Volume, cm^3	5.77 (1.51)	5.91 (1.49)	.703
MCA, cm^2	0.68 (0.32)	0.69 (0.25)	.893
Nasal cytology			
Eosinophil classes			.255
None (score=0)	10 (31%)	16 (50%)	
Few scattered cells (score=1)	8 (25%)	5 (16%)	
Moderate number (score=2)	12 (38%)	7 (22%)	
Large clusters (score=3)	2 (6%)	4 (12%)	
Neutrophil classes			.223
None (score=0)	15 (47%)	21 (66%)	
Few scattered cells (score=1)	2 (6%)	2 (6%)	
Moderate number (score=2)	4 (12%)	5 (16%)	
Large clusters (score=3)	11 (34%)	4 (12%)	
T5SS total score	8.56 (2.7)	8.21 (2.56)	.591
PSQI total score	7.28 (1.89)	6.79 (3.13)	.446
PRQLQ total score	3 (1.21)	2.74 (1.13)	.383

Abbreviations: CTZ, cetirizine; nBDP, nasal beclomethasone dipropionate; MCA, minimal cross-sectional area; PRQLQ, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; PSQI, Pittsburgh Sleep Quality Index; T5SS, Total 5-Symptom Score.
[a]Data are presented as mean (SD) for quantitative variables, No. (%) for categorical variables.
[b]*t* test for quantitative variables; χ^2 test for categorical variables.

density, and the baseline value of the outcome. Comparisons were performed based on the least square mean change (LSmc) (*R* package *emmeans*).

Statistical significance was set at *P*<.05. The statistical analyses were performed using R version 3.4.2.

Results

Descriptive Statistics

Of the 128 screened patients, 60 were excluded owing to violation of the entry criteria or detection of exclusion criteria (Figure 1). Overall, 65 of the 68 randomized children (96%) completed the study. In particular, of the 34 patients randomized to CTZ, 31 completed the study: 1 patient (3%) withdrew consent, and 2 children (6%) were lost to follow-up (change of residence). All the 34 patients randomized to nBDP completed the study. Demographic characteristics and current environmental exposures (previous 12 months) were similar between the 2 groups at baseline (Table 1). Baseline values of the primary and secondary outcomes were also comparable (Table 2).

Eosinophil classes were negatively correlated with volume (Kendall τ, –0.21; *P*=.003) and MCA (Kendall τ, –0.14; *P*=.040) for both groups at both visits (Figure 2), while correlations between acoustic rhinometry parameters and all the subjective scores were not statistically significant.

For children who completed the study, the level of adherence was 100% in both treatment groups, no adverse events were observed, and no concomitant medication use was reported.

Primary Outcome

The exploratory analysis showed that volume values increased significantly after 21 days in the nBDP group (*P*=.033), while the change was not significant in the CTZ group (*P*=.900) (Figure 3, top panels). Similarly, MCA values increased significantly in the nBDP group (*P*=.045), while the change was not significant in the CTZ group (*P*=.840) (Figure 3, bottom panels). After adjusting for confounders, nBDP was found to improve nasal volume more than CTZ (LSmc, 2.21 cm^3 vs 0.20 cm^3; *P*=.013) (Table 3). Similarly, nBDP improved MCA more than CTZ (LSmc, 0.63 cm^2 vs 0.13 cm^2; *P*=.002).

doi: 10.18176/jiaci.0263

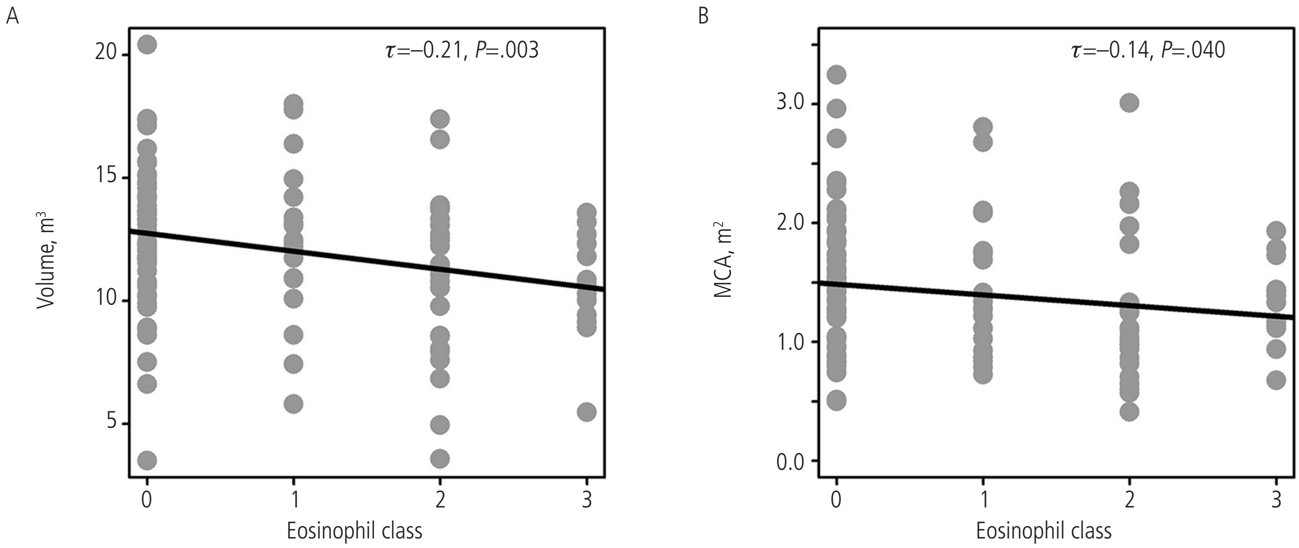

Figure 2. Correlations between acoustic rhinometry (A, Volume; B, MCA) and eosinophil classes in the CTZ and nBDP groups at the baseline and post-treatment visits. For both groups at both visits eosinophil classes were negatively correlated with volume (Kendall τ, –0.21, *P*=.003) and MCA (Kendall τ, –0.14, *P*=.040). MCA indicates minimum cross-sectional area.

Secondary Outcomes

In the nBDP group, with respect to the CTZ group, a more pronounced improvement was observed in eosinophil classes (LSmc, –1.10 vs –0.40, *P*=.031) and neutrophil classes (LSmc, –0.97 vs –0.17; *P*=.010), T5SS total score (LSmc, –5.63 vs –3.54; *P*=.008), PSQI total score (LSmc, –1.30 vs –0.19; *P*=.025), and PRQLQ total score (LSmc, –1.15 vs –0.69; *P*=.031) (Table 3).

Discussion

The present study demonstrates that a 21-day course of treatment with nBDP is more effective than oral CTZ for improving nasal patency as measured using acoustic rhinometry in children with PAR.

Despite its feasibility and noninvasiveness, acoustic rhinometry is not extensively used in children, probably because of the weak correlation with self-reported nasal congestion [25,26], which was also shown in the present study. The very few studies that have evaluated acoustic rhinometry for assessment of PAR in children are characterized by differences in the study design and the INCs administered [16,17,27]. Since none of these studies evaluated the effect of nBDP, the findings of the present study can be only partially compared with previous results.

We observed significant improvements in nasal volume in the first 5 cm from the nostril and in MCA, thus indicating the anti-inflammatory effect of nBDP. The reported effects were expressed in terms of LSmc, which represents the predicted means of the outcomes in a hypothetical population of patients with a balanced (uniform) distribution of the variables included in the model, specifically, age, weight, current exposure to smoke, mold, dog/cat dander, traffic density, and baseline value of the variable of interest. As a result, LSmc is expressed in the same unit of measurement as the outcomes and, therefore, has real, direct clinical significance. As highlighted by Straszek et al [10], the sensitivity of volume parameters to changes in nasal patency has to be ascribed to the change in mucosal swelling. However, previous studies reported somewhat discordant findings. In particular, a similar result was observed by Wandalsen et al [17], where the authors evaluated the effect of a 21-day course of once-daily mometasone furoate 100 µg and found a significant increase in all of the acoustic rhinometry parameters investigated, as well as a decrease in the nasal symptom score. In contrast, de Andrade et al [27] did not observe significant differences in nasal cavity volume after a 6-week course of fluticasone propionate.

nBDP was also found to improve nasal volume and MCA to a greater extent than CTZ. Even though INCs and antihistamines have been assessed in placebo-controlled trials in children with PAR [16,28], their effect on nasal patency has not been explicitly compared. In the present study, the greater effect of nBDP in comparison with CTZ was also corroborated by the higher reduction in counts of nasal inflammatory cells, such as eosinophils and neutrophils. This reinforces the results of a placebo-controlled study [29], which did not include an antihistamine arm, thus providing more evidence of the efficacy of nBDP in decreasing the chronic inflammation of the upper airways in patients monosensitized to the perennial allergen *D pteronyssinus*.

The current study also integrates previous findings about the efficacy of nBDP in improving symptom severity in children [30] and adolescents [31] with PAR, as well as its effect on quality of life [31] and sleep quality [32,33]. Specifically, nBDP was found to improve the T5SS, PSQI, and PRQLQ scores more than CTZ. Of note, none of the available

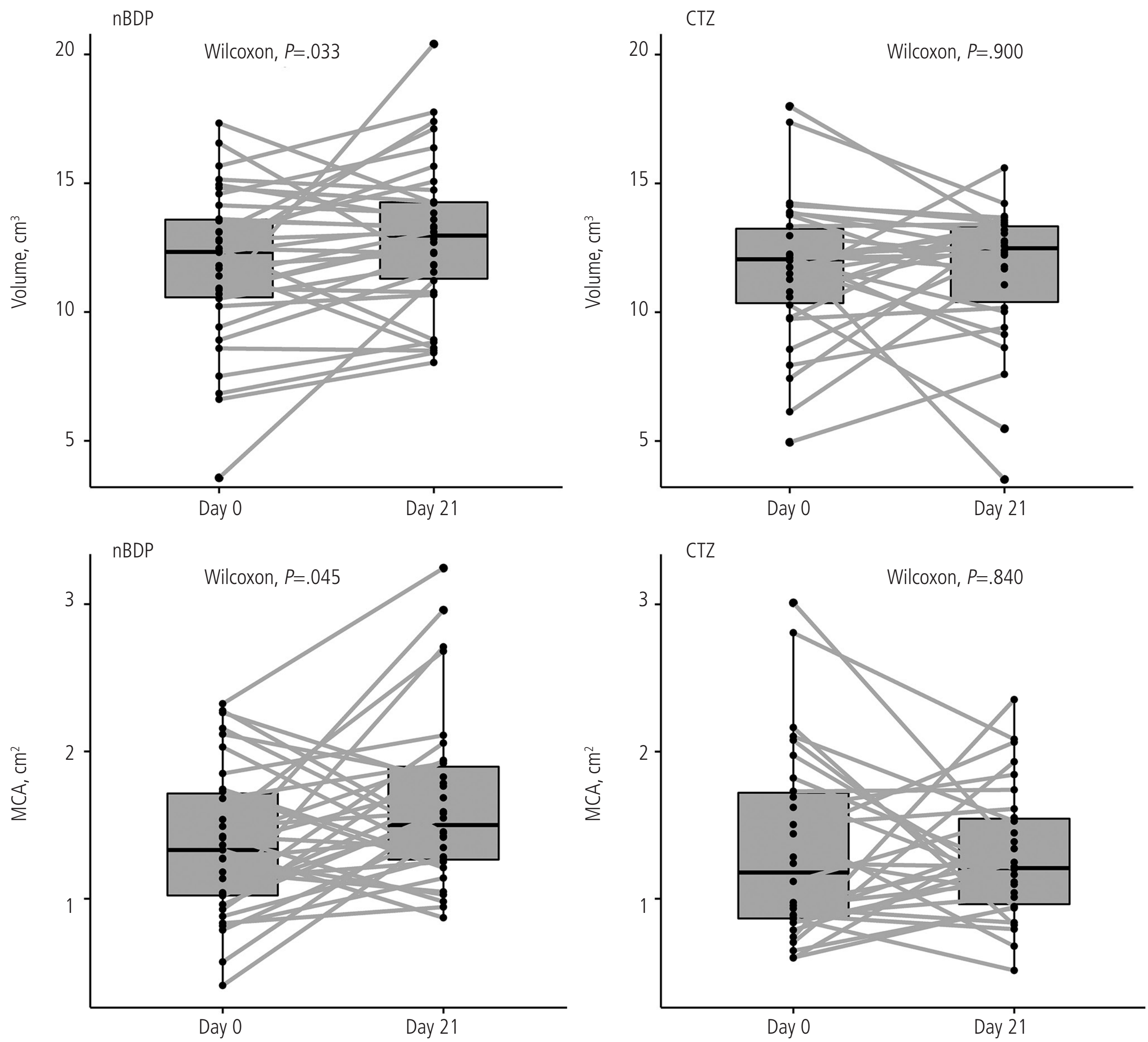

Figure 3. Volume and MCA values at the baseline and post-treatment visits for the 2 study groups. After 21 days, volume values increased significantly in the nBDP group (*P*=.033) compared with a nonsignificant change in the CTZ group (*P*=.900) (top panels); MCA values increased significantly in the nBDP group (*P*=.045) compared with a nonsignificant change in the CTZ group (*P*=.840) (bottom panels). CTZ indicates cetirizine; nBDP, nasal beclomethasone dipropionate.

studies investigating the effect of different treatments on nasal patency used a comprehensive approach including subjective outcomes such as sleep quality and quality of life [16,17,27]. The importance of assessing these parameters in clinical practice has been emphasized as part of a holistic approach that can also be adopted when treating children. In fact, it is well known that the symptoms of PAR can negatively affect children's activities and sleep quality, leading to daytime somnolence and fatigue [34].

The main novelty of our study is the comparative investigation of the effect of topical nBDP and oral CTZ on nasal patency in children with PAR measured using acoustic rhinometry and other objective and subjective outcomes. In fact, the more pronounced effect of nBDP in comparison with CTZ was supported by concomitant improvements in nasal cytology and in scores for nasal symptom severity, quality of life, and sleep quality. Such comprehensive assessment may prove useful in the clinical management of children with PAR.

Even if 3 patients dropped out of the CTZ group (31 completed the study), this did not affect the desired power of the study, since 30 patients per group would have been enough (see *Sample Size*). Another positive aspect is

doi: 10.18176/jiaci.0263

Table 3. Mean Change From Baseline in Variables of Primary and Secondary Interest Over the Treatment Period[a]

	CTZ (n=31)	nBDP (n=34)
Volume, cm^3		
LS mean change (*P* value)	0.10 (.810)	1.11 (.039)
LS mean change difference (*P* value)		1.01 (.013)
MCA, cm^2		
LS mean change (*P* value)	0.06 (.441)	0.31 (.002)
LS mean change difference (*P* value)		0.25 (.002)
Eosinophil classes		
LS mean change (*P* value)	–0.40 (.202)	–1.10 (.008)
LS mean change difference (*P* value)		–0.70 (.031)
Neutrophil classes		
LS mean change (*P* value)	–0.17 (.565)	–0.97 (.016)
LS mean change difference (*P* value)		–0.80 (.010)
T5SS total score		
LS mean change (*P* value)	–3.54 (<.001)	–5.63 (<.001)
LS mean change difference (*P* value)		–2.09 (.008)
PSQI total score		
LS mean change (*P* value)	–0.19 (.706)	–1.30 (.050)
LS mean change difference (*P* value)		–1.11 (.025)
PRQLQ total score		
LS mean change (*P* value)	–0.69 (.003)	–1.15 (<.001)
LS mean change difference (*P* value)		–0.46 (.031)

Abbreviations: CTZ, cetirizine; LS, least square; MCA, minimal cross-sectional area; nBDP, nasal beclomethasone dipropionate; PRQLQ, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; PSQI, Pittsburgh Sleep Quality Index; T5SS, Total 5-Symptom Score.
[a]Models were adjusted for age, weight, current exposure to smoke, mold, dog/cat dander, traffic density, and baseline value of the variable of interest.

the very good adherence to daily treatment (100% in both groups), thanks to close telephone follow-up by well-trained investigators. nBDP treatment was also well tolerated, and no adverse events were observed.

The main limitation of the present study is the fact that patients and investigators were not blinded to treatment. However, this may not have affected the results owing to the objective nature of the primary outcomes (and concordant results found for the secondary outcomes). Our study is also limited by the absence of an objective evaluation of drug safety. We did not perform such an evaluation in the light of the results of a recent study on nasal treatment with nBDP, which failed to show a significant systemic effect in treated children with PAR [35]. The lack of hypothalamus-pituitary-adrenal axis suppression may be attributable to the low systemic bioavailability of nBDP resulting from low absorption through respiratory and digestive mucus membranes [36].

Conclusions

The current study demonstrated the greater effect of nBDP in comparison with CTZ on nasal permeability measured using acoustic rhinometry in children with PAR. Similarly, a greater anti-inflammatory effect of nBDP resulted in reduced nasal inflammatory cell counts. Moreover, nBDP proved to be effective in reducing the subjective burden perceived by patients, with beneficial effects on symptom severity, quality of life, and sleep quality.

Funding

The study was supported by CHIESI Farmaceutici S.p.A., Parma, Italy (Unrestricted Grant N. 3774/2015).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Roberts G, Xatzipsalti M, Borrego L, Custovic A, Halken S, Hellings P, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2013;68:1102-16.
2. Valero A, Navarro A, Del Cuvillo A, Alobid I, Benito J, Colás C, et al. Position paper on nasal obstruction: evaluation and treatment. J Investig Allergol Clin Immunol. Published Online First: 2018. doi:10.18176/jiaci.0232

3. Jessen M, Malrn L. Definition, prevalence and development of nasal obstruction. Allergy. 1997;52:3-6.
4. Baiardini I, Villa E, Rogkakou A, Pellegrini S, Bacic M, Compalati E, et al. Effects of mometasone furoate on the quality of life: a randomized placebo-controlled trial in persistent allergic rhinitis and intermittent asthma using the Rhinasthma questionnaire. Clin Exp Allergy. 2011;41:417-23.
5. Ciprandi G, Mora F, Cassano M, Gallina AM, Mora R. Visual analog scale (VAS) and nasal obstruction in persistent allergic rhinitis. Otolaryngol Neck Surg. 2009;141:527-9.
6. Zicari AM, Occasi F, Giulia M, Indinnimeo L, De Castro G, Tancredi G, et al. Intranasal budesonide in children affected by persistent allergic rhinitis and its effect on nasal patency and Nasal Obstruction Symptom Evaluation (NOSE) score. Curr Med Res Opin. 2015;31:391-6.
7. Nathan RA, Eccles R, Howarth PH, Steinsvåg SK, Togias A. Objective monitoring of nasal patency and nasal physiology in rhinitis. J Allergy Clin Immunol. 2005;115:S442-59.
8. Uzzaman A, Metcalfe DD, Komarow HD. Acoustic rhinometry in the practice of allergy. Ann Allergy Asthma Immunol. 2006;97:745-52.
9. Wandalsen G, Mendes A, Matsumoto F, Solé D. Acoustic rhinometry in nasal provocation tests in children and adolescents. J Investig Allergol Clin Immunol. 2016;26:156-60.
10. Straszek SP, Schlunssen V, Sigsgaard T, Pedersen OF. Reference values for acoustic rhinometry in decongested school children and adults: the most sensitive measurement for change in nasal patency. Rhinology. 2007;45:36.
11. Malizia V, Fasola S, Ferrante G, Cilluffo G, Montalbano L, Landi M, et al. Efficacy of Buffered Hypertonic Saline Nasal Irrigation for Nasal Symptoms in Children with Seasonal Allergic Rhinitis: A Randomized Controlled Trial. Int Arch Allergy Immunol. 2017;174:97-103.
12. Ferrante G, Fasola S, Cilluffo G, Malizia V, Montalbano L, Landi M, et al. Nasal budesonide efficacy for nasal nitric oxide and nasal obstruction in rhinitis. Pediatr Allergy Immunol. 2017;28:393-7.
13. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140:950-8.
14. Ferrante G, Montalbano L, Cilluffo G, Malizia V, Marchese D, La Grutta S. Beclomethasone dipropionate hydrofluoroalkane for the treatment of allergic rhinitis. Expert Rev Clin Immunol. 2016;12:279-88.
15. Nunes C, Ladeira S. Double-blind study of cetirizine and loratadine versus placebo in patients with allergic rhinitis. J Investig Allergol Clin Immunol. 2000;10:20-3.
16. Yaşar M, Uysal I, Altuntaş EE, Cevit Ö, Müderris S. Effects of topical sprays on allergy-induced nasal obstruction in children. Kulak Burun Bogaz Ihtis Derg KBB J Ear Nose Throat. 2013;23:217-24.
17. Wandalsen GF, Mendes AI, Sole D. Objective improvement in nasal congestion and nasal hyperreactivity with use of nasal steroids in persistent allergic rhinitis. Am J Rhinol Allergy. 2010;24:e32-e36.
18. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens W, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008. Allergy. 2008;63:8-160.
19. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008;100:S1-S148.
20. Clement P, Gordts F. Consensus report on acoustic rhinometry and rhinomanometry. Rhinology. 2005;43:169-79.
21. Gelardi M, Iannuzzi L, Quaranta N, Landi M, Passalacqua G. NASAL cytology: practical aspects and clinical relevance. Clin Exp Allergy. 2016;46:785-92.
22. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.
23. Juniper EF, Howland WC, Robertsa NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol. 1998;101:163-70.
24. Cibella F, Cuttitta G, La Grutta S, Melis MR, Lospalluti ML, Uasuf CG, et al. Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. Pediatr Allergy Immunol. 2011;22:60-8.
25. Scadding G, Hellings P, Alobid I, Bachert C, Fokkens W, van Wijk RG, et al. Diagnostic tools in Rhinology EAACI position paper. Clin Transl Allergy. 2011;1:2.
26. Öztürk F, Türktaş İ, Asal K, İleri F, Pınar NM. Effect of intranasal triamcinolone acetonide on bronchial hyper-responsiveness in children with seasonal allergic rhinitis and comparison of perceptional nasal obstruction with acoustic rhinometric assessment. Int J Pediatr Otorhinolaryngol. 2004;68:1007-15.
27. de Andrade CR, Chatkin JM, Fiterman J, Scaglia N, Camargos PA. Unified disease, unified management: treating allergic rhinitis and asthma with nasally inhaled corticosteroid. Respir Med. 2010;104:1577-80.
28. Guilemany JM, García-Piñero A, Alobid I, Centellas S, Mariño FS, Valero A, et al. The loss of smell in persistent allergic rhinitis is improved by levocetirizine due to reduction of nasal inflammation but not nasal congestion (the CIRANO study). Int Arch Allergy Immunol. 2012;158:184-90.
29. Van As A, Bronsky EA, Dockhorn RJ, Grossman J, Lumry W, Meltzer EO, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone diproprionate. J Allergy Clin Immunol. 1993;91:1146-54.
30. Berger WE, Jacobs RL, Amar NJ, Tantry SK, Li J, Small CJ. Efficacy and safety of beclomethasone dipropionate nasal aerosol in children with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2015;115:130-6.
31. Meltzer E, Jacobs R, LaForce C, Kelley C, Dunbar S, Tantry S. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. Allergy Asthma Proc. 2012;33:249-57.
32. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1990;86:380-6.
33. Milgrom H, Biondi R, Georgitis JW, Meltzer EO, Munk ZM, Drda K, et al. Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children. Ann Allergy Asthma Immunol. 1999;83:105-11.
34. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest. 2000;118:372-9.

doi: 10.18176/jiaci.0263

35. Hampel FC, Nayak NA, Segall N, Small CJ, Li J, Tantry SK. No hypothalamic-pituitary-adrenal function effect with beclomethasone dipropionate nasal aerosol, based on 24-hour serum cortisol in pediatric allergic rhinitis. Ann Allergy Asthma Immunol. 2015;115:137-42.
36. Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. Br J Clin Pharmacol. 2001;51:400-9.

Salvatore Fasola

National Research Council of Italy
Institute of Biomedicine and Molecular Immunology "A. Monroy"
Via Ugo La Malfa 153, 90146 Palermo, Italy
E-mail: salvatore.fasola@ibim.cnr.it