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ISSN 0946-1965

DOI 10.5414/CP202100
e-pub: July 30, 2014

A novel therapeutic use of HFA-BDP metered-dose inhaler in asthmatic patients with rhinosinusitis: Case series

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Key words

airway medicine– asthma – exhalation through the nose – rhinosinusitis – small airway obstruction

Abstract. Objective: Most asthmatics have been found to have rhinosinusitis (RS). Patients with ethmoid sinusitis, in particular, often suffer from an impaired sense of smell; this is clinically important and necessitates concurrent treatment for both asthma and RS. As a rational therapeutic strategy, we focused on a fine particle HFA-134a-beclomethasone dipropionate (HFA-BDP) metered-dose inhaler. Because of its small size, the medication is still present in the exhaled breath after inhalation. Methods: Five mild-to-moderate asthmatics with ethmoid-predominant sinusitis characterized by an impaired sense of smell and mild peripheral blood eosinophilia received a single-agent treatment with orally-inhaled HFA-BDP which was then exhaled through the nose. In addition, the stained small particles were created by an ultrasonic nebulizer and flow image of them during oral inhalation and nasal exhalation was evaluated by using nasal endoscopy. Results: After treatment, the sense of smell was restored in all cases with a concomitant improvement in sinusitis as confirmed by computerized tomography. In addition, amelioration of peripheral blood eosinophilia as well as small airway obstruction as indicated by pulmonary function tests was observed. Macroscopical imaging revealed that small particles flow toward olfactory cleft during both the inhalation and exhalation phases. Conclusion: We have presented 5 cases of asthmatic patients with RS treated with a concurrent single therapy, HFA-BDP exhaled through the nose (ETN). A clinical trial must be considered to establish this new therapeutic strategy based on the concept of “one airway, one disease.”

BAAs) [1]. Despite effective treatment strategies, its prevalence is still increasing. Further, many asthmatics have rhinosinusitis (RS) as demonstrated by computed tomography (CT) scans [2] and they suffer from nasal obstruction or impaired sense of smell. Pfister et al. [3] observed mucosal thickening of sinuses on CT scans in 74% of asthmatic patients. Along with the abnormalities of sinus on CT scans, patients with severe asthma also have eosinophilia in peripheral blood and induced sputum, impaired pulmonary function, and elevated levels of exhaled NO [4]. Furthermore, patients with severe asthma tend to have more severe RS [5, 6]. Therefore, recognizing the close relationship between asthma and RS is crucial for asthma control.

For simultaneous treatment of both asthma and RS based on the concept of “one airway, one disease”, we previously evaluated the hydrofluoroalkane-134a-beclomethasone dipropionate (HFA-BDP) metered-dose inhaler. This inhaler contains an extra-fine particle, which remains in the expired breath due to its small size (average diameter: 1.1 μ m) [7, 8]. To optimally use HFA-BDP, we examined its beneficial effect when it was orally-inhaled and then exhaled through the nose (ETN) on a trial basis. In our preliminary study, HFA-BDP ETN converted from the conventional ICS therapy (equivalent doses of fluticasone propionate or HFA-BDP) improved both small airway obstruction and nasal symptoms (such as nasal obstruction and impaired sense of smell) along with the improvement in sinus CT findings [9]. However, in that study we could not exclude the possibility of synergistic effects with other medications such as LABAs or leukotriene receptor antagonists. Here, we report a series of 5 cases of bronchial asthma with RS treated with the single-agent therapy using HFA-BDP ETN.

Introduction

Bronchial asthma, a chronic inflammatory airway disease, can be well controlled by the regular use of inhaled corticosteroids (ICS) with or without long-acting β_2 -agonists (LA-

Received
December 13, 2013;
accepted
May 5, 2014

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Table 1. Clinical characteristic of 5 cases.

Case no.	1	2	3	4	5	Mean $\pm$ SD
Age/sex	69/F	60/F	71/F	69/F	60/F	65.8 $\pm$ 5.4
Severity of asthma	mild	moderate	mild	moderate	moderate	
Smoking status	never	never	never	never	never	
Total IgE (IU/mL)	122	99	237	325	218	200 $\pm$ 92
Eosinophil (/ μ L)	595	596	310	312	760	515 $\pm$ 198
FEV ₁ (L)	1.71	1.36	1.64	1.60	1.53	1.57 $\pm$ 0.13
%FEV ₁ (%)	89.6	69.6	84.9	86.7	70.4	80.2 $\pm$ 9.5
Reversibility						
Δ FEV ₁ (mL)	280	260	320	240	230	266 $\pm$ 36
Δ FEV ₁ (%)	16.4	19.4	21.6	17.6	15.0	18.0 $\pm$ 2.6
FVC (L)	2.42	2.00	2.21	2.34	2.07	2.21 $\pm$ 0.18
FEV ₁ % (%)	70.7	68.0	74.2	68.4	73.9	71.0 $\pm$ 2.9
%FEF ₂₅₋₇₅ (%)	46.0	30.6	53.1	40.3	39.2	41.8 $\pm$ 8.4
ACT	24	18	24	25	22	22.6 $\pm$ 2.8
LMS						
Total	9	10	8	12	9	9.6 $\pm$ 1.5
Ethmoid	5	4	4	5	4	4.4 $\pm$ 0.5
Pretreatment						
ICS (μ g)/LABA	0/–	0/–	200/+	400/+	0/–	
LTRA	–	+	–	–	–	

FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; FEF₂₅₋₇₅ = forced expiratory flow between 25% and 75% of vital capacity; ACT = asthma control test; LMS = Lund-Mackay scale; ICS = inhaled corticosteroid (equivalent doses of fluticasone propionate); LABA = long-acting β_2 -agonist; LTRA = leukotriene receptor antagonist.

Methods

Subjects

Five patients with mild-to-moderate asthma, determined according to the Global Initiative for Asthma (GINA) guidelines [10], were evaluated. They all were never-smokers with positive reversibility and had mild eosinophilia, evidence of small airway obstruction, and an impaired sense of smell due to RS, caused predominantly by CT-confirmed ethmoid sinusitis (evaluated using the Lund-Mackay scale). Two patients were receiving no medication, another patient used only a leukotriene receptor antagonist, and the other two had been treated with conventional ICS/LABA treatment which was orally-inhaled and exhaled through the mouth. No patients had received any treatments, such as topical corticosteroids or endoscopic sinus surgery, for RS. All patients were converted to a single-agent therapy using HFA-BDP ETN without a wash out period for the pre-treatment and continued on only HFA-BDP ETN without any concomitant treatment. Briefly, HFA-BDP (QVAR, 3M Pharmaceuticals, St. Paul, MN, USA; 400 μ g twice a day) was inhaled orally using

a spacer (VORTEX[®], PARI-Japan, Osaka, Japan), followed by breath-holding for a few seconds and exhalation through the nose. We confirmed the procedures at the beginning of HFA-BDP ETN treatment and on each visit to make sure that patients were able to perform them properly. Two patients had diabetes or hypercholesterolemia, and the other three did not have any comorbidity requiring treatment. The patient characteristics are summarized in Table 1. All patients gave their written informed consent for inclusion in this report.

Macroscopic imaging

Normal saline solution was stained with natural dye (Kiriya's brilliant green SP, KIRIYA Chemical Co., Ltd. Osaka, Japan). Three healthy volunteers orally inhaled the small particles (a single-digit μ m range) created by an ultrasonic nebulizer, followed by breath-holding for a few seconds and exhalation through the nose. The particle flow during oral inhalation and nasal exhalation was observed by using nasal endoscopy. All healthy volunteers gave their written informed consent for inclusion in this study.

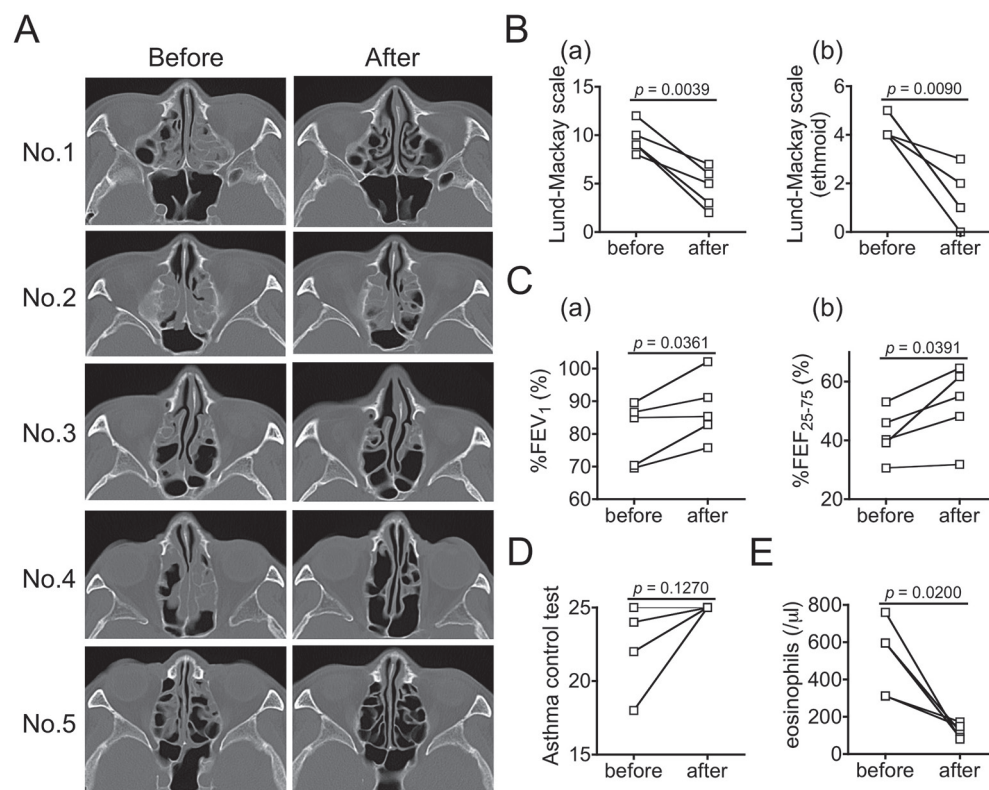


Figure 1. Effects of HFA-BDP ETN treatment. All 5 patients inhaled HFA-BDP using a tube-type spacer, followed by exhalation through the nose. Each parameter was evaluated before and after treatment with HFA-BDP ETN (Case no. 1, 3, and 5: 2 months after treatment; Case no. 2: 4 months after treatment; Case no. 4: 1 month after treatment). The indicated periods depend on the first visit after converting to HFA-BDP ETN. A: CT findings in the sinus; B: Lund-Mackay scale (panel a: total score; panel b: ethmoid sinus score). Comparisons of data before and after treatment were performed using a paired t-test; C: Lung function test (panel a: %FEV₁; panel b: %FEF₂₅₋₇₅); D: Asthma control test; E: Peripheral blood eosinophil counts.

Results

After the commencement of HFA-BDP ETN therapy, the restoration of their sense of smell with concomitant improvement in the Lund-Mackay scale was observed within 2 months in 4 patients (Figure 1A, B). Furthermore, HFA-BDP ETN treatment also provided good asthma control, as evaluated by the Asthma Control Test with decreased airway obstruction including small airways, as shown by improvements in forced expiratory volume in 1 second (%FEV₁) and forced expiratory flow between 25% and 75% of vital capacity (%FEF₂₅₋₇₅) (Figure 1C, D). These results were supported by the amelioration of mild eosinophilia linked to asthma as well as RS with ethmoid-predominant sinusitis (Figure 1E). Four patients had no recurrence of symptoms with continued HFA-BDP ETN treatment. The dose of HFA-BDP was successfully tapered for one

of these patients (case no. 4). Another patient stopped the HFA-BDP treatment because of mild treatment-induced stomatitis; the discontinuation resulted in the recurrence of RS and asthma symptoms after 4 months (case no. 2).

In macroscopic examination, we found that small particles flow toward the olfactory cleft during both the inhalation and exhalation phases (Figure 2).

Discussion

As shown in our case series, a rational and simultaneous therapy for asthma and RS is required based on the concept of “one airway, one disease”. Nonaka et al. [11] recently reported a case of refractory RS with comorbid asthma successfully treated with orally-inhaled fluticasone propionate (FP). They speculated that inhaled FP (100 μg twice a

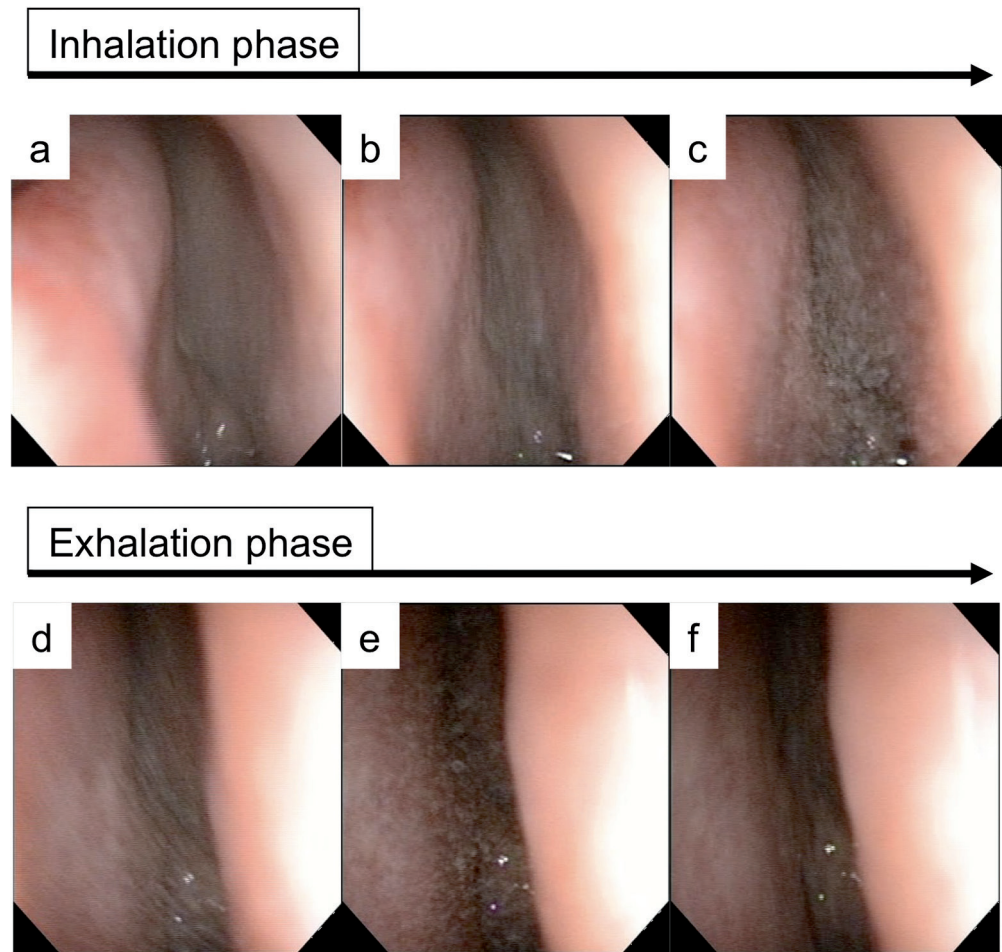


Figure 2. Time-lapse flow images of small particles from the inhalation phase to the exhalation phase. Small particles (a single-digit μm range) made by an ultrasonic nebulizer were inhaled orally and exhaled through the nose. Flow images towards the olfactory cleft were serially observed from inhalation phase (upper; a – c) to exhalation phase (lower; d – f) every second using nasal endoscopy. Panels a and f show the middle meatus at the beginning of the inhalation phase (a) and the end of the exhalation phase (f). Panels b and d show the flow lines of particles towards the olfactory cleft (from bottom to top). Panels c and e show the clusters of particles floating in the middle meatus for 1 s.

day) attenuated lower airway inflammation mainly associated with eosinophils, resulting in an amelioration of recurrent RS following endoscopic sinus surgery [11]. However, in our case (no. 4), RS could not be controlled even with the administration of higher doses of orally-inhaled FP (200 μg twice a day). In the case reported by Nonaka et al. [11], it is possible that the distribution of orally-inhaled FP to the ethmoid sinus mucosa may have been enhanced by endoscopic sinus surgery [12].

RS with ethmoid-predominant sinusitis characterized by activated eosinophil infiltration is associated with olfactory dysfunction [13]. This explains why the amelioration of ethmoid sinusitis as confirmed by CT led to a restoration of the sense of smell in the pa-

tients evaluated in this study. Scheibe et al. [14] indicated that drug delivery to the olfactory cleft provides a beneficial effect on the restoration of sinonasal smell disorders. To confirm whether the small particles (a single-digit μm range) flow toward the olfactory cleft during oral inhalation and nasal exhalation, we observed the particles by using nasal endoscopy. Macroscopical imaging revealed that small particles easily and effectively reach the olfactory cleft during both the inhalation and exhalation phases. This finding may explain not only the lasting improvement of olfactory impairment by HFA-BDP ETN but also the beneficial effects with the conventional orally-inhaled ICS in some cases, such as that reported by Nonaka et al. [11]. However, Hyo et al. [15] has shown that only

3% of the small particles (μm range) reach the paranasal sinuses, supporting our previous report that the conventional orally-inhaled and orally-exhaled HFA-BDP did not improve RS [9]. In the cases without endoscopic sinus surgery, continuous treatment with HFA-BDP ETN may increase the accumulation into paranasal sinuses, resulting in suppression of airway inflammation. Beneficial effects of topical nasal corticosteroids for patients with RS have been demonstrated [16, 17] whereas in our case series, all patients improved by single-agent HFA-BDP ETN therapy. Intranasal administration using a squirt system could efficiently deliver corticosteroids to the olfactory cleft, thereby exerting a beneficial effect on olfactory dysfunction; however, these effects are incomplete and transient [18]. It is notable that the conversion from conventional ICS to HFA-BDP ETN (equivalent doses of ICS) provided beneficial effects for patients with poorly controlled asthma with RS even under treatment with ICS and intranasal corticosteroid [9].

RS with ethmoid-predominant sinusitis is closely related to bronchial asthma and peripheral blood eosinophilia [19]. As peripheral blood eosinophil counts correlate with infiltrating eosinophil counts in nasal polyps [19], we confirmed decreased peripheral blood eosinophil counts with concomitant improvement in sinus CT findings after treatment. Even after converting from conventional ICS/LABA therapy to HFA-BDP ETN, asthma in these patients was well-controlled without exacerbation which reflected the decreased eosinophil counts in the peripheral blood. Furthermore, HFA-BDP inhibited eosinophilic inflammation in the small airways of asthmatics more potently compared with an equivalent dose of FP treatment [20]. In addition, latent small airway inflammation has a close relationship with RS [21], suggesting that it is important to regulate inflammation of both small airway and paranasal sinuses. We believe that HFA-BDP ETN therapy may be a reasonable option due to the small particle size, which is capable of reaching both the small airways and olfactory cleft (or paranasal sinuses) and control both upper and lower airway inflammation more effectively.

Since the sample size in this case report was too small to conclude beneficial effect of HFA-BDP ETN treatment, a crossover study

or a blinded placebo-controlled study need to be done to confirm our preliminary findings.

Conclusion

We have reported 5 cases of asthmatic patients with RS (ethmoid-predominant sinusitis) treated with HFA-BDP ETN. A clinical trial must be conducted to confirm the utility of this novel strategy based on the concept of “one airway, one disease”.

Consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Funding

No funding.

Conflict of interest

The authors declare that they have no competing financial interests.

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