ORIGINAL ARTICLE

COMPARISON OF ORAL AND LARYNGEAL FINDINGS OF ASTHMA PATIENTS USING DIFFERENT DRY POWDER INHALER DEVICES CONTAINING STEROID AND BETA AGONISTS

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ABSTRACT

Objective: In this study, we aimed to compare the oral and laryngeal findings of asthma patients using different dry powder inhalers (DPI) containing corticosteroid and long-acting beta-2 agonists.

Methods: This study included 109 asthmatics who were divided into 3 groups according to the inhaler device (Seretide Discus [fluticasone 250 mcg, salmeterol 50 mcg], Symbicort Turbuhaler [budesonide 320 mcg, formoterol 9 mcg], and Foradil [formoterol 12 mcg] + Miflonide [budesonide 400 mcg] aerolizer), and compared with 34 healthy controls. Oral and laryngeal regions were examined comprehensively by a rigid telescope.

Results: While frequency of oral candidiasis was higher in the group taking budesonide + formoterol by an aerolizer than those of other DPI using groups, frequency of laryngeal candidiasis was more elevated in asthma patients compared to those of healthy controls ($p<0.05$). Frequency of vocal fold hyperemia and edema was lower in asthma patients taking budesonide + formoterol combination by a Turbuhaler compared to those of other DPI using groups ($p<0.05$), it was higher in asthmatics than that of healthy controls, and it was also determined to be higher in asthmatics with dysphonia compared to that of asthmatics with a normal voice ($p<0.05$).

Conclusion: In the present study, a high rate of oral and laryngeal abnormalities was determined in asthmatics using DPI with a lower rate in asthmatics taking budesonide + formoterol by a Turbuhaler. Further studies with more comprehensive oral and laryngeal examinations before and after treatment may provide more information on this aspect.

Key Words: asthma, steroids, inhalation devices, laryngeal findings.

INTRODUCTION

Inhaled steroids are very important drugs recommended for treatment of all stages of persistent asthma.[1] Inhaled steroids reduce airway inflammation and hyperreactivity in asthma and decrease the frequency and severity of asthma attacks along with probably attenuating the remodeling of airway.[1]

Best known and most common side effects of inhaled steroids are dysphonia and oral candidiasis.[2] Lately, budesonide which is known to be an inhaler steroid for asthma patients has been reported to increase the oropharyngeal gram negative colonization in patients above age of 50 years and FEV_1 below 70%.[3] Following the use of metered dose inhalers (MDIs) for asthma treatment, recently, lactose-based dry powder inhalers (DPIs) have been produced and eventually become available and widespread. A study showed lactose-based DPIs to reduce salivary pH significantly more than MDIs[4] effects of different lactose-based DPIs have not been compared for their side effects on oropharynx and larynx. In the present study, we aimed to compare the oral and laryngeal side effects of different lactose-based DPIs used on asthma patients.

PATIENTS AND METHODS

Study population

One hundred and nine asthma patients who were diagnosed in the outpatient clinic of the Department of Chest Disease at Abant Izzet Baysal University, Turkey, were enrolled in the study, and compared with 34 healthy volunteers prospectively recruited from the general population. Normal health status was defined as the absence of known diseases as assessed by a systematic medical interview, general physical examination performed by one of the authors. Written informed consent was taken from all participants. Diagnosis, grading, and treatment of asthma patients were carried out ac-

cording to GINA guideline[1] Lactose-based DPI using patients were divided into 3 groups each of which included usage of a different DPI device twice a day as follows: Seretide Diskus (salmeterol xinafoate 50 mcg; fluticasone propionate 250 mcg), Symbicort Turbuhaler (formoterol 9 mcg; budesonide 320 mcg), and Miflonide (budesonide 400 mcg) + Foradil (formoterol 12 mcg) via aerolizer. People that have been using inhaler steroid for at least 2 months were included in the study. Oropharynx and larynx of the patients who have been diagnosed with asthma by Chest Diseases Polyclinic and started to be treated previously, were examined in detail by an Ear Nose Throat (ENT) specialist using rigid telescope. Moreover, ID data, duration of disease, severity of disease, and atopy status of patients were recorded from their files. This study was approved by the Ethical Committee of Izzet Baysal Medical Faculty, Bolu, Turkey.

Oral and Laryngeal Examination

Oropharyngeal and comprehensive larynx examinations of all the patients were carried out by an ENT specialist via a rigid telescope of 70^0–90^0 angles (Karl Storz Tuttlingen, Germany). Results were recorded as clinical presence or absence of oral and laryngeal candidiasis, vocal fold hyperemia, and edema in larynx.

Exclusion criteria

Patients with diabetes mellitus, gastroesophageal reflux disease, chronic pulmonary disease, hematological malignancies, congestive heart failure, chronic renal failure, severe bronchiectasis, history of tuberculosis, history of lung, ear, nose, and throat operation, patients with upper and lower respiratory infections, patients who had been taking systemic antibiotics within the last months and systemic or inhaled steroids within the last 4 weeks, patients who were on proton pump inhibitor and antacid therapy, and smokers were excluded from the study. Patients who had mucosal disorders such as lichen planus were excluded by dermatological examination.

Statistical Analysis

Statistical analysis was done using SPSS statistical software program version 10.0 (SPSS Inc., Chicago, IL). T test and an ANOVA test were used to compare quantitative variables. Pearson's Chi-square was used to determine independence between paired variables, with significance set at $p<0.05$.

RESULTS

109 asthma patients using different DPI devices and 34 healthy controls were included in the study. Mean age, gender distribution of asthma patients and healthy control group, and presence of atopy and severity of disease in asthma patients, were showed in Table 1.

Table 1: Characteristics of patients and healthy controls [n (%)]

	Miflonide + Foradil aerolizer (n=42)	Seretide discus (n=33)	Symbicort turbuhaler (n=34)	Healthy control group (n=34)
Median age ± SD*	54.9 ± 14.2	53.3 ± 14.8	52.5 ± 17.2	49.7 ± 13.2
Mean duration of asthma symptoms (month)	98.9 ± 100	94.5 ± 97.1	79.8 ± 86.6	
Mean duration of medication (month)	16.98 ± 25.65	14.55 ± 22.27	12.56 ± 21.78	
Gender				
Female	30 (71.4)	22 66.7)	18 (52.9)	21 (61.7)
Male	12 (28.6)	11 (33.3)	16 (47.1)	13 (38.3)
Presence of atopy	12 (28.6)	7 (21.2)	8 (23.5)	
Severity of disease [1]				
Moderate	29 (69.0)	24 (72.7)	28 (82.3)	
Severe	13 (31.0)	9 (27.3)	6 (17.6)	

* Standard deviation

Table 2: Oral and laryngeal findings of asthmatics using different DPI

		Oral candidiasis	Vocal fold hyperemia	Vocal fold edema	Laryngeal candidiasis
	n	n (%)	n (%)	n (%)	n (%)
Miflonide + Foradil aerolizer	42	7 (16.7)*	9 (21.4)	9 (21.4)	7 (16.7)
Seretide discus	33	2 (6.1)	9 (27.3)	10 (30.3)	3 (9.1)
Symbicort turbuhaler	34	0	1 (2.9)*	2 (5.9)*	1 (2.9)
Total	109	9 (8.3)	19 (17.4)#	21 (19.4)#	11 (10.2)#
Healthy control group	34	1 (2.9)	1 (2.9)	1 (2.9)	0

*$p<0.05$, compare to other's DPI; #$p<0.05$, compare to healthy control group

Frequency oral candidiasis was higher in asthma patients taking Miflonide (budesonide 400 mcg) + Foradil (formoterol 12 mcg) via an aerolizer than those of other asthma patients using DPI ($p<0.05$). Frequency of vocal fold hyperemia and edema were lower in Symbicort turbuhaler using group compared to those of other DPI users ($p<0.05$). Frequency of laryngeal candidiasis was more elevated in asthma group than in control group ($p<0.05$). Frequency of vocal fold hyperemia and edema was significantly higher in asthma group than that of control group ($p<0.001$) (Table 2).

No difference was found between oral and laryngeal results regarding gender difference in asthma patients using different DPIs ($p>0.05$). Frequency of laryngeal candidiasis was higher in asthma patients above age of 50 years compared to that of patients aged below 50 years ($p<0.05$). Frequency of vocal fold hyperemia and edema was significantly elevated in asthma patients with dysphonia compared to that of patients without dysphonia ($p<0.001$) (Table 3).

Table 3: The oral and laryngeal findings according to gender, age, presence of dysphonia in asthma patients

		Oral candidiasis	Vocal fold hyperemia	Vocal fold edema	Laryngeal candidiasis
	n	n (%)	n (%)	n (%)	n (%)
Gender					
Male	39	6 (8.6)	13 (15.4)	14 (17.9)	3 (7.7)
Female	70	3 (7.7)	6 (18.6)	7 (20.0)	8 (11.4)
Age group					
< 50	39	1 (2.6)	8 (20.5)	9 (23.1)	1 (2.6)
≥ 50	70	8 (11.4)	11 (15.7)	12 (17.2)	11 (14.3)#
Dysphonia					
Absent	81	6 (7.4)	6 (7.4)	7 (8.6)	7 (8.6)
Present	28	3 (10.7)	13 (46.4)*	14 (50.0)*	4 (14.3)
Total	109	9 (8.3)	19 (17.4)	21 (19.4)	11 (10.2)

# $p<0.05$, * $p<0.001$

DISCUSSION

Fukushima *et al.* [5] found higher amount of isolated Candida in asthma patients using fluticasone propionate diskhaler than that of asthma patients using beclomethasone MDI by a spacer. Bousquet *et al.*[6] reported no difference of oral candidiasis frequency between asthma patients taking mometasone furoate by DPI and asthma patients taking budesonide via turbuhaler. Dubus *et al.*[7] determined esophageal candidiasis frequency (37%) in asthma patients using inhaler fluticasone propionate, significantly higher than that of control group (0.3%). In the present study, frequency of laryngeal candidiasis was higher in asthma patients compared to that of controls. Frequency oral candidiasis was found to be higher in asthma patients taking budesonide + formoterol via an aerolizer. Particularly, despite receiving almost the equivalent doses of the same active ingredient via aerolizer and turbuhaler, the different frequencies of oral and laryngeal candidiasis obtained in this study were notable. That may be occurring due to properties of Turbuhaler device. Turbuhaler device assorts the active ingredient in thinner particles and transfers them to lungs without permitting them to be stored in oropharyngeal and laryngeal regions at considerable amounts. Jackson *et al.*[8] reported that Metered dose inhaler (MDI) or a Turbuhaler reduces oropharyngeal deposition and increases lung deposition. Moreover, each budesonide and formoterol capsule using aerolizer contains 25 mcg lactose per dose.[9] Lactose amount is 12.5 mcg per dose for Seretide Discus device[10], and less than 1 mcg for Turbuhaler[11]. High lactose content of budesonide and formoterol taken via aerolizer, may be enabling higher uptake of steroid in oral and laryngeal regions, leading to stimulation of candidiasis development. Pharmacological examination of the storage of steroids used by 3 different devices in oropharyngeal and laryngeal regions, may contribute to the explanation of this subject.

Oral candidiasis is commonly seen in the elderly. Tanida *et al.*[12] revealed that the decreases of salivary flow rates and salivary anti-candidal factors, suppression of salivary neutrophil function and the increase of candidal adhesion sites on keratinocytes predispose elderly individuals to oral candidiasis. While in our study frequency of oral and laryngeal candidiasis were found to be higher in asthma patients above age of 50 compared to the patients below 50 ages, solely frequency of laryngeal candidiasis was statistically significant.

In the present study, frequency of vocal fold hyperemia and edema was low in asthma patients without dysphonia and who were using Symbicort turbuhaler. Moreover, frequency of vocal fold hyperemia and edema was more elevated in asthma patients compared to that of healthy control group. Ihre *et al.*[13] demonstrated that there is a positive correlation between voice problems and inhalation of corticosteroids. Williamson *et al.*[14] found dysphonia or throat symptom frequency in asthma patients using inhaler steroid to be higher and reported indifference between beclomethasone dipropionate and budesonide aerosol inhaler users regarding the side effects. Lavy *et al.*[2] examined 22 patients using inhaler steroid and having dysphonia problem with videostrobolaryngoscopy. Among those patients had 58% mucosal changes, 43% apposition abnormalities, 40% supraglottic hyperfunction, 39% mucosal wave abnormalities, and 73% shortening of maximal phonation time. Krecicki *et al.*[15] reported frequency of vocal fold bowing and atrophy of laryngeal mucosal to be higher in asthma patients who have used inhaler steroids for at least 18 months, compared to the healthy control group. Mirza *et al.*[16] examined laryngeal region of 10 asthma patients presented with dysphonia despite using fluticasone and salmeterol containing DPI, by videostroboscope. In eight of nine patients, they revealed areas of hyperemia in the vocal folds, with plaque-like changes on the surface mucosa. In addition, they found reduced amplitude of vibration and a reduction in mucosal wave

propagation by videostroboscopy. Roland *et al.*[17] reported DPIs as containing high dose of lactose and causing cough after inhalation. In the present study, we believe that the lower frequency of vocal fold hyperemia and edema in Symbicort Turbuhaler using patients may be due to properties of Turbuhaler device and its low level of lactose. The results of our study indicate that oral and laryngeal disorders may arise in majority of asthma patients using inhaler steroids via DPI. Particularly, in studies which investigate the efficiency of inhaler steroids, determination of the local side effects of the drugs is carried out mostly by depending on the expressions of the patients, therefore, we believe those abnormalities are not always mentioned by patients. However, examinations conducted by an ENT specialist can reveal oral and laryngeal abnormalities more frequently in patients using those drugs.

In conclusion, in the present study, a high rate of oral and laryngeal abnormalities was determined in asthma patients using DPI. Frequency of vocal fold hyperemia and edema was determined to be lower in asthma patients taking budesonide + formoterol by a Turbuhaler. Further studies including more comprehensive oral and laryngeal examinations before and after treatment may provide more detailed information on this subject.

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