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Original Article

The Frequency and Risk Factors for Oropharyngeal Candidiasis in Adult Asthma Patients Using Inhaled Corticosteroids

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Abstract

OBJECTIVES: Worldwide, asthma is a major health problem and inhaled corticosteroids (ICS) are the mainstay of asthma treatment. High-dose and long-term use of ICS can result in some side effects. The present study aimed to determine the frequency of oral and systemic candidiasis infections in adult asthma patients using ICS, and to identify possible risk factors.

MATERIAL AND METHODS: This study included 186 randomly selected adult asthma patients that presented to allergy clinic between May 2011 and September 2012.

RESULTS: Among the patients, 147 (79%) were female. The lifelong incidence of oral candidiasis was 19.4% (n=36), whereas 5.38% (n=10) of the patients already had it by the time of the study. The lifelong incidence of any fungal infection was 59.7% (n=111). There weren't any significant differences in gender, age, age at onset of asthma, oral hygiene, atopy, or comorbid diseases between the oropharyngeal candidiasis (OPC)-positive and -negative groups. A history of persistent rhinitis, use of a leukotriene receptor antagonist together with ICS, and use of ciclesonide as an ICS were associated with a higher incidence of OPC.

CONCLUSION: In the present study the incidence of OPC in adult asthma patients was quite high, but no definitive risk factors were identified. Further studies are needed to distinguish these individual differences.

KEYWORDS: Oropharyngeal candidiasis, asthma, inhaled corticosteroids, side effects, asthma treatment

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways that remains a serious health problem affecting an estimated 300 million people worldwide. Inhaled corticosteroids (ICS) are currently the most effective anti-inflammatory medi- cations for the treatment of persistent asthma [1]. Research has shown that ICS are effective for reducing asthma symp- toms, improving quality of life, improving lung function, decreasing airway hyperresponsiveness, controlling airway inflammation, reducing the frequency and severity of exacerbations, and reducing the incidence of asthma-related mortality. ICS cause some systemic (decreased bone mineral density, skin atrophy and bruising, cataracts, and impaired growth in children) and local side effects when used at high doses and long term [2]. Oropharyngeal candidiasis (OPC), dysphonia, lingual hypertrophy, cough, xerostomia, altered taste perception, gingivitis, halitosis, dental caries, and pharyngitis are among the common local side effects of ICS [3,4]. The frequency of OPC varies according to the type and dosage of inhaled corticosteroid (ICS) used [5,6]. An ideal ICS has minimal deposition in the oropharynx and maximal deposition in the lungs. All of these side effects are usually infrequent and seem to be minor problems, but they can cause clinical discomfort and alter compliance to treatment [7].

Deposition of ICS in the oropharyngeal cavity can cause OPC; this occurs due to decreased local immunity involving inhibition of normal host defense functions (neutrophils, macrophages, and T-lymphocytes) at the oral mucosal surface or because of an increase in the salivary glucose level, which stimulates growth of candida albicans [8]. The aim of the present study was to determine the frequency of oropharyngeal and systemic candidiasis infections in adult asthma patients using ICS treatment and to identify possible risk factors for OPC.

MATERIALS AND METHODS

This cross-sectional study included 186 adult asthma patients that presented to our adult allergy clinic between May 2011 and September 2012. Consecutive patients diagnosed as persistent asthma that were regular using ICS treatment for ≥ 6

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Table 1. Patient demographic characteristics

	n	%
Mean age (years)	49.96±15.0	
Sex		
Female	147	79
Male	39	21
Mean age of onset of asthma (years)	36.1±15.57	
Additional atopic disease	147	79
Comorbid diseases		
Diabetes mellitus	18	9.7
History of OPC	36	19.4
History of other fungal infections		
Nail	20	10.8
Inguinal	6	3.2
Foot	19	10.2
Vaginal	42	28.6
Others	14	7.5

months were included in the study. Epidemiological data (demographic data), additional atopic (persistent rhinitis, seasonal rhinitis, urticaria, and dermatitis) and comorbid (diabetes mellitus, hypertension, gastroesophageal reflux, depression, and obesity) diseases, oral hygiene (dry mouth, dental caries, mouth rinse status), all lifelong history of fungal infections (oropharyngeal, nail, inguinal, foot, vaginal, skin, etc.), and medications used for infections and asthma were recorded using a questionnaire administered by a trained physician.

Concomitant use of 2 different ICS, or inhaled and oral corticosteroids together was defined as combined corticosteroid treatment. Atopy was defined as ≥ 1 positive skin prick tests. Skin prick testing to aeroallergens included pollens (*Phleum pratense, Artemisia vulgaris, Parietaria officinalis, Corylus avellana, Olea europaea, Betula verrucosa*), *Dermatophagoides pteronyssinus, Acarus siro, Lepidoglyphus destructor*, and *Tyrophagus putrescentiae*, molds (*Aspergillus fumigatus, Cladosporium herbarum*, and *Alternaria alternata*), animal dander (dog and cat), and *Blatella* allergen. The study protocol was approved by local ethics committee (Hacettepe University School of Medicine 01,03,2013 B.30.2.HAC.0.05.07.00/224). Verbal informed consent was obtained from patients.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences v.18.0 (IBM SPSS Statistics Corp.; Armonk, NY, USA) for Windows. The usual statistical tests were performed for univariate analysis. Between-group comparison of qualitative variables was performed via the Chi-square test and quantitative variables were compared using the t-test. The level of statistical significance was set at $p<0.05$.

RESULTS

Among the 186 patients, 147 (79%) were female and 39 (21%) were male. Mean age of the patients was 49.96±15.0 years

Table 2. Comparison of patients with and without OPC

	OPC positive	OPC negative	p
Sex	n (%)	n (%)	0.264
Female	26 (17.7)	121 (82.3)	
Male	10 (25.6)	29 (74.4)	
Mean age (years)	49.25±15.86	50.13±14.83	0.752
Mean age of onset of asthma (years)	35.09±17.2	36.34±15.2	0.679
Dry mouth	21 (19.1)	89 (80.9)	0.913
Dental caries	16 (30.2)	37 (69.8)	0.057
Mouth rinse			0.414
Regularly	27 (18.5)	119 (81.5)	
Intermittent	3 (15)	17 (85)	
No rinse	6 (30)	14 (70)	
Additional atopic disease			0.106
Negative	4 (10.3)	35 (89.7)	
Positive	32 (21.8)	115 (78.2)	
Persistent rhinitis	29 (22)	103 (78)	0.158
Seasonal rhinitis	5 (20)	20 (80)	0.93
Atopy (n= 122)	11 (20)	44 (80)	0.934
Comorbid diseases			0.3
Diabetes mellitus	5 (27.8)	13 (72.2)	0.341
Obesity	4 (11.8)	30 (88.2)	0.215
GE reflux	16 (21.3)	59 (78.7)	0.575
Treatment			0.021
Only CS	5 (10)	45 (90)	
CS + β-mimetics	9 (17.3)	43 (82.7)	
CS + montelukast	12 (37.5)	20 (62.5)	
CS + β-mimetics+ montelukast	10 (19.2)	42 (80.8)	
Combined CS			0.025
Negative	32 (18)	146 (82)	
Positive	4 (50)	4 (50)	
ICS type			0.003
Beclomethasone	5 (35.7)	9 (64.3)	
Budesonide	18 (15.7)	97 (84.3)	
Fluticasone propionate	9 (18.4)	40 (81.6)	
Ciclesonide	4 (80)	1 (20)	
Mometasone furoate	0 (0)	3 (100)	
Other fungal infections			
Nail	2 (10)	18 (90)	0.262
Inguinal	2 (33.3)	4 (66.7)	0.378
Foot	4 (21.1)	15 (78.9)	0.843
Vaginal	10 (23.8)	32 (76.2)	0.379
Others	3 (21.4)	11 (78.6)	0.847

CS: Corticosteroid, ICS: Inhaled corticosteroids

(range: 16-89 years) and mean age of onset of asthma was 36.1±15.57 years. In all, 147 (79%) of the patients had ≥1 additional atopic diseases. The lifelong incidence of oral candidiasis was 19.4% (n=36), whereas 5.38% (n=10) already had it at the time of the study. The lifelong incidence of any type of fungal infection was 59.7% (n=111), whereas 6.4% (n=12) already had one at the time of the study (Table 1).

There weren't any significant differences in gender (p=0.264), age (p=0.752), age of onset of asthma (p=0.679), additional atopic diseases (p=0.106), diabetes mellitus (p=0.341), obesity (p=0.215), gastroesophageal reflux (p=0.575), dry mouth (p=0.913), dental caries (p=0.057), mouth rinse status (p=0.414), or atopy (p=0.934) between the OPC-positive and OPC-negative groups (Table 2). Among the 26 patients with a history of vaginal candidiasis following antibiotic use, only 7 had a history of OPC. There weren't any significant differences between a history of vaginal candidiasis after antibiotic usage and OPC. A history of persistent rhinitis (p=0.034), use of a leukotriene receptor antagonist together with an ICS, and use of ciclesonide as an ICS (p≤0.001) were associated with an higher frequency of (≥2) OPC infection (Table 3).

DISCUSSION

In the present study the incidence of OPC in adult asthma patients was quite high (19.7), but no definitive risk factors were identified. According to the literature, the incidence of OPC (infection or colonization) in adult asthma patients ranges from <1% to 70%, depending on the diagnostic criteria used [8]. The variability in the incidence of OPC might also be the result of the fact that OPC does not always cause symptoms; only 33% of patients with OPC complain of sore throat or hoarseness. One review reported that OPC occurred in ≤ 5% of adult patients receiving ICS, of which ≥25% had positive mouth cultures [9].

The incidence of OPC can vary with ICS formulation, dose, and dosing frequency [10,11]. An increased risk of OPC has also been associated with concomitant use of oral corticosteroids, antibiotics, and diabetes medications [12]. In the present study the use of combined corticosteroid treatment was associated with an increase in the frequency of OPC, whereas comorbid diabetes mellitus was not. According to Turkish and international guidelines, a moderate dose of ICS in combination with a leukotriene receptor antagonist is recommended for patients with moderate-severe asthma [1,13]. Use of a leukotriene receptor antagonist together with ICS was associated with an increased frequency of OPC in the present study, which might have due to the fact that most of the included patients had moderate-severe asthma and were receiving high-dose, long-term ICS treatment. Pinto et al. reported a cross-sectional study that included 200 moderate or severe asthma patients and observed no statistically significant difference between the groups of patients with and without self-reported adverse effects for any of charactersitcs (age, sex, dose of ICS, use of dry powder inhaler and metered dose inhaler, duration of ICS use, nasal corticosteroid use, oral hygiene after ICS use) and in terms of frequency of local symptoms between medium and high doses of ICS using patients [14]. Intrinsic inflammation of the upper airways in

Table 3. Characteristics according to OPC frequency

	0 n (%)	1 n (%)	≥ 2 n (%)	p
Sex				0.618
Female	121 (82.3)	10 (6.8) 1	6 (10.9)	
Male	28 (75.7)	4 (10.8)	5 (13.5)	
Treatment				0.099
Only CS	44 (89.8)	1 (2)	4 (8.2)	
CS + β-mimetics	43 (84.3)	4 (7.8)	4 (7.8)	
CS + montelukast	20 (62.5)	5 (15.6)	7 (21.9)	
CS + β-mimetics + montelukast	42 (80.8)	4 (7.7)	6 (11.5)	
CS type	9 (64.3)	1 (7.1)	4 (28.6)	< 0.001
Beclomethasone				
Budesonide	96 (85)	10 (8.8)	7 (6.2)	
Fluticasone propionate	40 (81.7)	3 (6.1)	6 (12.2)	
Ciclesonide	1(20)	0	4 (80)	
Mometasone furoate	3 (100)	0	0	
Combined CS	4 (50)	1 (12.5)	3 (37.5)	0.044
Additional atopic diseases	114 (73.1)	12 (8.2)	20 (13.7)	0.116
Persistent rhinitis	102 (77.9)	9 (6.9)	20 (15.2)	0.034
Seasonal rhinitis	20 (80)	1 (4)	4 (16)	0.597
Dermatitis	6 (66.7)	2 (22.2)	1 (11.1)	0.235

CS: Corticosteroid, ICS: Inhaled corticosteroids

asthma patients, mechanical irritation caused by coughing, concomitant inflammatory diseases (e.g. rhinitis), and concomitant inflammatory environmental factors (e.g. air pollution) may also have an effect on the local side effects of ICS [7]. In the present study a history of persistent rhinitis was associated a history of OPC.

Many ICS (i.e. fluticasone propionate and budesonide) are inhaled in their pharmacologically active form, whereas other ICS (ciclesonide and beclomethasone dipropionate) are inhaled as inactive compounds and are activated by esterases in the lungs. Such on-site activation is important for reducing the potential local side effects of ICS by limiting the availability of active drug beyond the target tissue [13].

Interestingly, in the present study frequent OPC infection was associated with use of ciclesonide as an ICS, which might have been the result of physicians prescribing ciclesonide to patients with a history of OPC.

The present study has some limitations, including its cross-sectional design and the fact that the types and doses of ICS at the time of OPC were not recorded. In addition, medications were recorded as current treatment and the diagnosis of OPC and systemic candidiasis was made according to patient reports.

In conclusion, the frequency of OPC in the present study's adult asthma patients receiving regular ICS treatment was quite high. OPC has a negative effect on patient quality of life and treatment compliance. Despite the fact that no risk fac- tors for OPC were identified in the present study, we think that asthma patients should be informed about this side-effect at the beginning of ICS treatment. Further studies are needed to distinguish these individual differences.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University School of Medicine (01,03,2013 B.30.2.HAC.0.05.07.00/224).

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