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ORIGINAL ARTICLE

Risk Factors of Local Oropharyngeal and Laryngeal Adverse Effects from Use of Single Inhaled Corticosteroids and Long-Acting Beta-Agonists

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ABSTRACT

Background: Single inhaled corticosteroids and long-acting beta-agonists (ICS/LABA) are clinically effective and safe. However, if local oropharyngeal and laryngeal adverse effects (LOLAE) appear, adherence to the use of ICS is impaired. To minimize the development of adverse effects, it is essential to identify the underlying risk factors.

Methods: The study included 481 asthmatic patients who were prescribed ICS/LABA for the first time in their life between January and September of 2010. Patients ranged in age from 14 to 86 years old and consisted of 281 never smokers and 200 smokers. All data were collected retrospectively by respirologists.

Results: Seventy-three out of 481 patients suffered from one or more adverse effects, with 54 of these exhibiting LOLAE. Patients with LOLAE (51.4 ± 16.2 yrs) were significantly older than those without LOLAE (43.7 ± 15.9 yrs) ($p = 0.0011$) and were also prescribed a significantly higher dose of ICS. The pack-years of patients with LOLAE (2.1 ± 4.9) were significantly lower than those without LOLAE (6.0 ± 13.0) ($p = 0.0087$). The type of administered ICS was also significantly associated with a risk of developing LOLAE.

Conclusions: Our survey indicated that a greater age, a higher dose of ICS, and the type of ICS were potential risk factors of LOLAE. The identified factors should be considered in a clinical setting in order to prevent the development of LOLAE and provide optimal treatment to patients.

KEY WORDS

adrenergic beta-agonists, adverse effects, asthma, glucocorticoids, metered-dose inhalers

INTRODUCTION

Asthma is a serious worldwide public health problem for all age groups and is characterized by chronic airway inflammation, which is associated with airway hypersensitiveness. Although the clinical manifestations of asthma can be controlled with appropriate treatment, if asthma is not treated properly, airway inflammation worsens, resulting in remodeling of the airway and irreversible airflow limitation. Corticosteroids are the most effective anti-inflammatory medication for bronchial asthma.[1] Notably, smaller amounts of inhaled corticosteroids (ICS) show clinical efficacy for asthma than that needed for oral corticosteroids; for example, it has been reported that 600 μg of budesonide (BUD) is equivalent to 10 mg of prednisolone (PSL).[2] The introduction of ICS has markedly reduced hospitalizations[3] and death from asthma.[4]

Further progress in asthma treatment has been achieved by the introduction of a combination therapy with ICS and long-acting beta-agonists (LABA). Such a combination therapy is considered beneficial for patients who have persistent asthma symptoms despite treatment with ICS.[5-7] Single-inhaler therapy with combined ICS/LABA is considered more clinically effective and well-tolerated than separate inhaler

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Table 1 Patient characteristics

	n	(%)
Male	206	(42.8%)
Female	275	(57.2%)
Smoking history		
Never Smokers	281	(58.4%)
Ex-Smokers and Current Smokers	200	(41.6%)
Mild Smokers (<20 pack year)	154	(32.0%)
Heavy Smokers (>=20 pack year)	46	(9.6%)
Pack-year (including Never Smokers)	5.59	±12.4
Bronchial asthma	274	(57.0%)
Cough variant asthma	207	(43.0%)
Duration since diagnosis (yr)	4.5	±9.7
Any previous treatment for asthma	169	(35.1%)
Type of ICS/LABA		
Budesonide/Formoterol	143	(29.7%)
Fluticasone/Salmeterol	338	(70.3%)
Daily dose of ICS (μg of fluticasone)	677	±320
Concomitant treatment		
Any one of the following	309	(64.2%)
Oral corticosteroid	162	(33.7%)
Leukotriene receptor antagonist	151	(31.4%)
Theophylline	157	(32.6%)
Short-acting β-agonist	63	(13.1%)

ICS/LABA, single inhaled corticosteroids and long-acting beta agonists; Daily dose of ICS (μg of fluticasone), budesonide dose was converted to half the dose of fluticasone.

therapy.[8,9] The main advantages of single-inhaler therapy are the improvement of adherence,[10-12] which is achieved by a simplified medication regimen, and patients' subjective symptomatic benefit following inhalation administration.

Although single-inhaler therapy with ICS/LABA is generally considered safe, local side effects, including oral laryngeal infection, hoarseness, and sputum, are often observed and may adversely influence patients' adherence.[13] Low medication adherence poses serious risks for asthma exacerbation, hospital admission, and even death.[14] Therefore, minimizing the development of adverse effects associated with ICS/LABA is essential for the successful treatment of asthma patients in a clinical setting. However, sufficient information concerning the potential risk factors for the adverse effects of ICS/LABA is currently unavailable.

The aim of the present study is to identify risk factors for the adverse effects of ICS/LABA to prevent LOLAE of ICS/LABA. Here, we retrospectively analyzed 481 asthma patients for a variety of factors to determine their association with the adverse effects of ICS/LABA.

METHODS

PATIENTS

The inclusion criteria for participation in this study were: (i) being prescribed budesonide/formoterol (B/F) or fluticasone/salmeterol (F/S) for the first time in one's life, (ii) not having been prescribed any ICS for the previous 12 months, and (iii) visiting the out-patient department of our hospital at least once for follow-up during the two months following the initial prescription. Patient lists were obtained from medical records of the Allergy and Respiratory Medicine Department at the Fraternity Memorial Hospital, Japan. Patients who were newly prescribed B/F or F/S between January and September 2010 were added to the list. Of the 902 patients included in the list, 387 were excluded for recent ICS prescription, 10 more were excluded because they did not have asthma, and 24 others were excluded because they did not visit for follow-up within the required period. Therefore, a total of 481 patients were ultimately enrolled in this study. The mean patient age was 44.5 ± 16.1 years (range: 14 to 86). The smoking status of the patients was as follows: 281 patients were classified as never smokers and 200 as current or ex-smokers. Concerning the diagnosis of asthma, 274 patients had bronchial asthma (BA) and 207 were diagnosed as having cough variant asthma (CVA). Detailed patient characteristics are summarized in Table 1.

STUDY DESIGN

All data were collected retrospectively from medical records and analyzed by respirologists. Any symptoms that satisfied the following criteria were included in the analysis: (i) potential adverse effects of ICS/LABA in the opinion of the respirologists, and (ii) symptoms that occurred in the first two months following the initial prescription of ICS/LABA. Smokers with a smoking history of 20 pack-years or more were classified as "heavy smokers," and all others were classified as "mild smokers." Spirometry was performed according to a standard protocol.[15] A dose potency ratio of 2 : 1 (fluticasone/budesonide) was adopted.[16,17] This study was approved by the Institutional Review Board of the Fraternity Memorial Hospital and patient anonymity was preserved at every stage of the study.

STATISTICS

Mann-Whitney's U test, Fisher's exact test, and Spearman's correlation coefficient by rank test were applied to data appropriately. All statistical analyses were performed using SSRI Excel Toukei 2010 (Japanese version).

RESULTS

Seventy-four out of 481 asthma patients (15%) suffered from one or more adverse effects during the

Table 2 Adverse effects occurring in asthma patients administered ICS/LABA

Adverse effect	*N*
Local oropharyngeal and laryngeal adverse effects	54†
hoarseness	19
laryngopharyngeal discomfort	14
sputum	11
sore throat	5
Candida thrush	4
stomatitis	2
glossitis	2
dysgeusia	2
laryngeal dryness	1
Other adverse effects	20
palpitation	9
tremor	3
nausea	3
rash	2
shoulder stiffness	1
chest pain	1
coughing	1

†Some patients have two or more adverse effects.

two-month period following administration of ICS/LABA. Fifty-four patients had local oropharyngeal and laryngeal adverse effects (LOLAE) and 20 experienced 'other' adverse effects. LOLAE consisted of hoarseness (n = 19), laryngopharyngeal discomfort (n = 14), sputum (n = 11), sore throat (n = 5), Candida thrush (n = 4), stomatitis (n = 2), glossitis (n = 2), dysgeusia (n = 2), laryngeal dryness (n = 1), and coughing (n = 1). A complete list of LOLAE and 'other' adverse effects is presented in Table 2.

Patients were divided into two groups: those with (n = 54) and without (n = 20) LOLAE. The patient characteristics between the groups were then compared and analyzed (Table 3). Patients in the LOLAE group were significantly older than those in the non-LOLAE group (51.4 ± 16.2 and 43.7 ± 15.9 years, respectively; p = 0.0011). The prescribed ICS dose was significantly higher in patients with LOLAE compared to those without (779 ± 328 and 664 ± 326 μg fluticasone, respectively; p = 0.0087). Regarding smoking history, patients with LOLAE had a significantly lower number of pack-years than those without LOLAE (2.1 ± 4.9 and 6.0 ± 13.0, respectively; p = 0.0087). No significant differences in duration between initial diagnosis of asthma and at the time of this study, FVC, FEV_1 and peak expiratory flow were detected between the two groups.

Next, the association between LOLAE and clinical parameters was evaluated with Fisher's exact test (Table 4). Patients with a history of oral corticosteroid administration had a higher incidence of LOLAE (16.7%) compared to those who had not received oral

Table 3 Risk factors for adverse effects of ICS/LABA

	Local oropharyngeal and laryngeal adverse effects		
	Yes	No	*p*
Total case number	54	427	
Age (yr)	51.4 ± 16.2	43.7 ± 15.9	0.0011**
Smoking history (pack years)	2.1 ± 4.9	6.0 ± 13.0	0.035*
Duration since diagnosis (yr)	4.8 ± 14.6	4.4 ± 9.8	0.21
Daily dose of ICS (μg as Fluticasone)	779 ± 328	664 ± 326	0.0087**
FVC (L)	2.9 ± 0.8	3.0 ± 0.9	0.68
FEV_1 (L)	2.4 ± 0.7	2.5 ± 0.8	0.48
Peak expiratory flow (L/sec)	6.5 ± 2.1	6.1 ± 2.1	0.24

Data are presented as mean ± standard deviation.
p values were calculated using Mann-Whitney's U test.
**$p < 0.01$, *$p < 0.05$.

corticosteroids (8.4%). A statistically significant association between oral corticosteroid administration and the development of LOLAE was detected (p = 0.0092, OR 2.16). A statistically significant association was also detected between a specific type of ICS (FP or BUD) and the appearance of LOLAE (p = 0.004, OR 0.32). No significant associations were found between any other clinical parameters and LOLAE (Table 4).

A cross table for the associations between LOLAE and ICS/LABA treatment, grouped by age and smoking history is shown in Table 5. The percentage of patients experiencing LOLAE increased with increasing age in never smokers and mild smokers. In contrast, the incidence of LOLAE in heavy smokers was only 3.3% (n = 30) in patients aged 40-59 and 0% (n = 16) in those aged 60-79.

DISCUSSION

Clarification of the risk factors of LOLAE for ICS is important for preventing LOLAE among asthma patients. In our present retrospective study of 481 asthma patients, we demonstrate that greater age, a higher dose of ICS, the type of ICS, concurrent use of oral corticosteroids, and smoking status are significantly associated with the occurrence of LOLAE. To evaluate the mechanisms underlying the association between LOLAE and the factors identified here, significant information regarding the prevention of LOLAE will be provided.

Patients of greater age experienced more LOLAE. This finding is supported by a previous report that showed older patients (≥65 years) more frequently complained of local adverse effects (hoarseness/dysphonia) than those of younger age groups.[18] Although it is presently unclear why elderly patients

Table 4 Risk factors for adverse effects of ICS/LABA

	Local oropharyngeal and laryngeal adverse effects				
				p	OR
Male/Female	24/206 (11.7%)		30/275 (10.9%)	0.88	1.07
NS/Smokers (ExS + CS)	37/281 (13.2%)		17/200 (8.5%)	0.14	1.63
Never/Mild/Heavy Smokers	37/281 (13.2%)	16/154 (10.4%)	1/46 (2.2%)	0.057	
CVA/BA	25/207 (12.1%)		29/274 (10.6%)	0.66	1.16
Any previous treatment for asthma (y/n)	15/169 (8.9%)		39/312 (12.5%)	0.29	0.68
BF/FS	7/143 (4.9%)		49/338 (13.9%)	0.004**	0.32
History of oral corticosteroid administration (y/n)	27/162 (16.7%)		27/319 (8.4%)	0.0092***	2.16
LTRA (y/n)	23/151 (15.2%)		31/330 (9.4%)	0.060	1.73
Theophylline (y/n)	21/157 (13.4%)		33/324 (10.2%)	0.36	1.36
Short-acting β-agonist (y/n)	5/63 (7.9%)		49/418 (11.7%)	0.52	0.65

p values were calculated using Fisher's exact test, with the exception of those for smoking history, which were calculated using the chi square test. $^{**}p < 0.01$, $^{***}p < 0.001$.

ICS/LABA, single inhaled corticosteroids and long-acting beta-agonists; OR, odds ratio; Daily dose of ICS (μg of fluticasone), budesonide dose was converted to half the dose of fluticasone; NS, Never Smokers; ExS, Ex-Smokers; CS, Current Smokers; Mild Smokers, smokers with a smoking history of <20 pack-years; Heavy Smokers, smokers with a smoking history of ≥20 pack-years; CVA/BA, cough-variant asthma/Bronchial asthma; BF/FS, budesonide + formoterol/fluticasone + salmeterol; LTRA, leukotriene receptor antagonist.

Table 5 Cross table for the association between ICS/LABA and local oropharyngeal and laryngeal adverse effects classified by age and smoking history

Smoking history	Age (yr)					Total
	≤19	20-39	40-59	60-79	≥80	
Never Smokers	0/14 (0.0%)	12/127 (9.4%)	10/74 (13.5%)	13/61 (21.3%)	2/5 (40.0%)	37/281 (13.2%)
Mild Smokers	0/0	3/80 (3.8%)	6/49 (12.2%)	7/24 (29.2%)	0/1 (0.0%)	16/154 (10.4%)
Heavy Smokers	0/0	0/0	1/30 (3.3%)	0/16 (0.0%)	0/0	1/46 (2.2%)
Total	0/14 (0.0%)	15/207 (7.2%)	17/153 (11.1%)	20/101 (19.8%)	2/6 (33.3%)	54/481 (11.2%)

Mild Smokers, smokers with a smoking history of <20 pack-years; Heavy Smokers, smokers with a smoking history of ≥20 pack-years.

display more LOLAE, it has been speculated that elderly people tend to have poor inhalation administration skills and forget or less frequently wash their mouth and pharynx after inhalation compared to younger patients. Furthermore, as elderly people typically experience age-related declines in immune function,[19] they are expected to have greater risk of Candida oropharyngitis.

Our analysis revealed that a higher percentage of patients using FP developed LOLAE compared to those receiving BUD. This finding is consistent with a previously reported finding in a systemic review.[20] On the other hand, the same author[20] demonstrated that data is available showing no difference in risk of oral candidiasis between FP and BUD. Although the reason underlying the identified association between FP and LOLAE is not clearly demonstrated, it is possible that the relationship is based on differences between the particle sizes of FP and BUD. It has been reported that the smaller particles of ICS reach

smaller airways, whereas larger particles only reach the upper airway.[21] Thus, as the particle sizes of FP are larger than those of BUD, FP would have a greater chance of adhering to the pharynx compared to BUD. In addition, it has been demonstrated that lactose combined with fluticasone facilitates deposition of particles in the upper airway.

A history of oral corticosteroid administration was also found to be a potential risk factor of LOLAE. In general, patients with more severe forms of asthma tend to more frequently receive temporary oral corticosteroid treatment for asthma exacerbations. Thus, the dose of ICS used by patients with a history of oral corticosteroid administration is likely higher than those without such a history, and may explain why this was identified as a risk factor of LOLAE in our analysis. Interestingly, we identified that patients with a more extensive smoking history had a lower incidence of LOLAE. The association between smoking status and the risk of LOLAE of ICS/LABA has not been reported yet. The underlying cause of the relationship requires careful interpretation. Although, with the data, it might be logical to consider that there might be a factor to prevent the development of LOLAE in smokers, it is more likely that smokers might not realize or report laryngopharyngeal discomfort or abnormal sensation of the larynx caused by ICS use, because they are accustomed to smoking-related troubles of the larynx. Ignoring early stage adverse events in smoking asthma patients may lead to the development of more severe adverse effects that are difficult to treat. Due to this possibility, doctors should more closely monitor for adverse effects of ICS when it is prescribed to smokers.

The difference in an occurrence of LOLAE between patients treated ICS/LABA and ICS only might be useful information for doctors. Although there are limited published data about the difference in an occurrence of LOLAE between patients treated ICS/LABA and ICS, from a clinical investigation, there were no difference in LOLAE between groups treated FP/sulbutamol and FP only.[22]

Here, we have provided important information concerning the potential risk factors of LOLAE that should be applied with care in the clinical treatment of asthma patients. In particular, doctors should not discontinue ICS/LABA just because a patient has a risk factor of LOLAE. LOLAE are preventable and reversible if they are identified at an early stage. It is recommended that doctors observe asthma patients in high-risk groups with extra care and provide information concerning the appropriate use of ICS/LABA, including mouth washing technique after inhalation, especially for elderly patients and/or those that receive high doses of ICS/LABA.

In this study, we found that a higher percentage of patients using FP experienced LOLAE compared to those receiving BUD. However, as it is generally known that FP is more powerful (per μg) than BUD, FP should not be changed to BUD solely based on the possibility of higher rates of LOLAE in patients who use FP. In fact, it has been reported that as the dose of FP increases, so do both the exacerbation prevention effects and the risk of oral candidiasis.[23] It is essential for doctors to decide which ICS/LABA is most suitable for individual patients based on a wide range of information, including disease severity, adherence, and risk factors for LOLAE.

In conclusion, greater age, a higher dose of ICS, and the type of ICS were identified as potential risk factors of LOLAE based on our retrospective survey. The apparent lower risk of LOLAE in smokers may be due to the tendency of these patients to not complain of discomfort even if they experience problems in the oropharynx and larynx. The identified factors should be considered in order to prevent LOLAE and provide optimal treatment to asthmatic patients.

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