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【 ORIGINAL ARTICLE 】

Influence of Adherence to Inhaled Corticosteroids and Inhaler Handling Errors on Asthma Control in a Japanese Population

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Abstract:

Objective High adherence to medications and accurate handling of inhaler devices are important for asthma management. However, few reports to date have simultaneously evaluated adherence and handling errors. We therefore investigated the adherence to inhaled corticosteroid (ICS) and inhaler handling errors in the same patients in cooperation with pharmacists.

Methods Data were derived from a survey of physicians and pharmacists treating asthma patients who visited participating hospitals and pharmacies from July 2012 to January 2013. The patients were evaluated for asthma control using the Asthma Control Test (ACT) and for inhaler handling errors using checklists. ICS adherence was evaluated based on pharmaceutical records.

Results Adherence among participants (n=290) was 33.3% (mean), and the percentage of inhaler handling errors was 20.0% (mean). Total inhalation times in the high-adherence group were fewer than those in the low-adherence group. In a comparison by device, adherence to pressurized metered dose inhalers was significantly lower than that to Diskus® inhalers, presumably attributable to the total number of inhalations per day. Adherence, handling errors, and total number of inhalations per day were significantly different between the asthma-controlled group and the uncontrolled group. A multivariate analysis showed that adherence and handling errors were independent factors contributing to asthma control.

Conclusion Our data indicated that both adherence to ICS and device handling errors contributed to asthma control in this population.

Key words: Asthma, adherence to inhaled corticosteroid, handling error, inhaler device

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Introduction

Bronchial asthma is characterized by chronic airway inflammation and reversible airway obstruction that is responsive to corticosteroids and bronchodilators (1). Inhaled corticosteroid (ICS) is the most efficacious agent for the control of airway inflammation and airway remodeling and the prevention of asthma death (2, 3). In our previous reports, symptom control and the frequency of exacerbation among asthma patients in Niigata Prefecture in Japan were improved by increased ICS usage based on a questionnaire survey (4-6). However, symptoms among some patients were still not controlled (6), meaning that unsolved problems persisted even after the introduction of ICS therapy.

The distribution of ICS to the bronchus and lung paren-

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chyma, patient adherence to medication, and inhaler handling errors are recognized as factors influencing ICS therapy (7). Based on these findings, adherence to medication and correct inhaler handling are central to the effective delivery of medication for asthma treatment.

The physician-patient relationship, convenience of medication usage, disease understanding, medication administration route, and frequency and time of usage are factors known to influence adherence to medications (8-10). In our previous report, the clinical predominance of fluticasone inhalation over beclomethasone inhalation was attributed to the former's superior adherence (11). Furthermore, we reported that adherence to medication correlated with age and gender (4) and was also dependent on the frequency and time of medication usage and concomitant medications (5).

With regard to inhalation techniques, the frequency of inhaler handling errors has been shown to correlate with age and disease severity (12). Another study reported that the likelihood of handling errors following brief training in device use differed among inhaler devices (13). A recent study of inhaler error data from a multicenter cross-sectional study of adult asthma patients reported that specific inhaler errors were identified as critical errors associated with poor control and exacerbation (14).

However, no study to date has investigated the adherence to medication and inhaler handling errors simultaneously in the same subjects and the involvement of these factors in asthma control. In this study, we retrospectively investigated the adherence to ICS treatment and ICS inhaler handling errors in the same patients in cooperation with pharmacists in Niigata Prefecture. The pharmacists calculated adherence to ICS and checked handling errors for inhaler devices according to a checklist. We also investigated whether or not adherence to ICS or ICS handling errors were influential on asthma control.

Materials and Methods

Subjects

The survey for this study was performed from July 2012 to January 2013 in accordance with the ethical principles for medical research involving human subjects and the Declaration of Helsinki and with the approval of the ethics committee of Niigata University (approval number 1231). The subjects were patients with a diagnosis of asthma from a physician, according to the guidelines of the Japanese Society of Allergology, who regularly used ICS dispensed by the pharmacies that participated in this survey. None of the subjects had changed their ICS prescription for at least 6 months prior to responding to the survey. Data from 343 patients were reviewed, and 53 patients were excluded because the data on adherence to ICS, ICS inhaler handling errors, or Asthma Control Test (ACT) scores were lacking. Therefore, 290 patients were enrolled in this study.

Protocol

After providing informed consent, patients completed a questionnaire on their age, gender, disease duration, duration of ICS use, ACT information, and the existence of exacerbation in the past year. In this study, the existence of any exacerbation was the only information collected from the patients; the questionnaire did not inquire about additional clinical background characteristics, such as the severity, frequency, and specific type of exacerbation. The size of the medical institution and the expertise of the attending physicians were also not included in the data.

The assessment of adherence to ICS and inhaler device handling errors

Adherence to ICS was assessed as described previously (15, 16). In brief, adherence to ICS was calculated by pharmacists based on the estimated total inhaler canisters prescribed in the previous six months (QE) according to information from physicians and the canisters actually prescribed to the patient during the same period (QA). Adherence was then expressed as a ratio, calculated using the following formula: QA/QE ×100 (% from 0 to 100). Adherence rates greater than 100 were expressed as 100 (modified adherence).

Pharmacists also checked for handling errors for inhaler devices used regularly among patients according to a checklist containing 10-15 checkpoints for each device (Supplementary material 1A-C). Handling errors were calculated by the ratio of inaccurate points to total checkpoints (% from 0 to 100).

In the analysis of adherence to ICS and inhaler handling errors, patients with at least the median value for the modified adherence rate were defined as the high-adherence group, and those with less than the median value for the modified adherence rate were defined as the low-adherence group. Similarly, patients with at least the median value for the handling error rate were defined as the high-handling-error group, and those with less than the median value for the handling error rate were defined as the low-handling-error group. Patients with at least the median value for ACT score were defined as the controlled group, and those with less than the median value for ACT score were defined as the uncontrolled group.

Statistical analyses

The results are expressed as means ± standard deviation (SD). To compare differences among the groups, Kruskal-Wallis tests and Dunn's multiple comparison tests were used. The Spearman correlation coefficient was used to assess the correlation between the two parameters. Between-group comparisons were performed using the Mann-Whitney test. A multivariate analysis was used to identify the variables that influenced asthma control. Variables that were statistically significant in the dichotomous analysis were subjected to the multivariate logistic regression analysis. Most

Table 1. Clinical Characteristics.

Patients (n)	290
Male, n (%)	131 (45.2)
Age (years)	61.1±16.6
BMI (kg/m²)	23.0±3.5
Disease duration (years)	13.1±13.6
ICS duration (years)	7.4±6.7
Never smoker, n (%)	146 (50.3)
Asthma Control Test	21.8±3.8
Exacerbation (%)	23.7
LABA (%)	76.2
Leukotriene modifier (%)	38.3
Theophylline (%)	25.2
Oral corticosteroid (%)	3.1
Modified adherence (%)	39.8±25.9
Handling error (%)	24.7±18.8
Total inhalation times (/day)	2.6±1.3

BMI: body mass index, ICS: inhaled corticosteroid, LABA: long-acting β agonist. Data are given as n (%) or means±standard deviation.

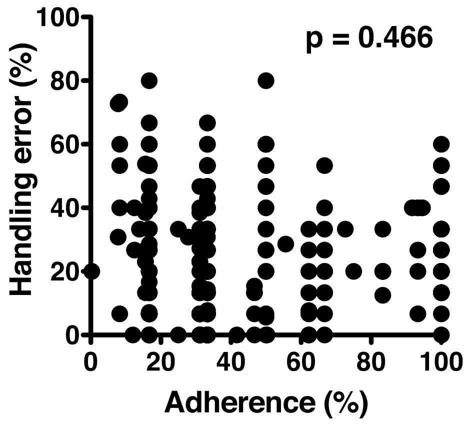

Figure. The association between adherence to inhaled corticosteroid (ICS) and inhaler handling errors. Adherence to ICS was calculated by comparing the prescribed medication with dispensed medication over a six-month period. The rates of inhaler device handling errors were determined using a checklist for each device type. The p value is indicated between the groups using the Spearman test.

statistical analyses were performed using the JMP software program, version 11 (SAS Institute, Tokyo, Japan). For all statistical analyses, p<0.05 was considered significant.

Results

The background data for participants are shown in Table 1. Among the 290 participants enrolled, 45% were men, the mean age was 61.4 years old, and the disease and ICS durations were 13.2 and 7.5 years, respectively. ACT scores were relatively high (mean ± SD: 21.8±3.8). In addition to ICS, approximately 75% of participants used a long-acting β agonist (LABA), mainly in combination with ICS. Only 3.1% of patients used oral corticosteroids regularly. Surprisingly, the modified adherence was extremely low (mean ± SD: 39.5±25.8%). The mean values of inhaler handling errors and total inhalation times were 24.6% and 2.5 times per day, respectively.

With regard to the correlation between adherence and handling errors, no significant correlation was observed between these parameters (Figure). Next, we compared subjects with modified adherence above the overall median (median: 33.3%; i.e. high-adherence group) to those with modified adherence below the median (i.e. low-adherence group). The disease duration and total inhalation time in the high-adherence group were longer and lower than those in the low-adherence group, respectively (Table 2A). We also compared subjects with fewer handling errors than the overall median (median: 20.0%; i.e. low-handling-error group) to those with more handling errors than the median (i.e. high-handling-error group) and observed no significant differences between the groups (Table 2B).

To determine whether there were differences among inhaler devices, we compared the background data for device usage. In this study, the distribution of inhaler device use was as follows: Diskus®, 58.8%; Turbuhaler®, 28.6%; pressurized metered dose inhaler (pMDI), 10.5%; and Twisthaler®, 1.4% (raw data not shown). In a comparison among Diskus®, Turbuhaler®, and pMDI, the total number of inhalations per day was significantly lower in the Diskus® group than in the Turbuhaler® and pMDI groups (Table 3). With regard to adherence among inhaler devices, the modified adherence for pMDIs was significantly lower than that for Diskus®, whereas the modified adherence for Turbuhaler® was not significantly different from that for Diskus® or pMDIs. The rates of handling errors did not differ markedly among the devices (Table 3).

In the checklist for inhaler handling, the actions of exhale, stop breathing after inhaling, and exhale were frequently associated with errors (Supplementary material 1A-C).

Next, we compared data from patients with ACT scores above the median (i.e. controlled group) with data from those with ACT scores below the median (i.e. uncontrolled group). Only data from participants using Diskus® and Turbuhaler® were used for this study, as pMDI use affected the adherence rates. The data for Twisthaler® were also excluded because of the low number of users of this device. Adjusted adherence (p=0.010), handling errors (p<0.001), and total number of inhalations per day (p=0.002) were significantly different between the controlled and uncontrolled groups (Table 4A).

In order to identify the factors affecting the ACT score, a multivariate analysis was performed, and the rates of adjusted adherence and handling errors were found to be independent factors contributing to asthma control, defined as an ACT score ≥23 (Table 4B). Furthermore, the modified adherence and handling errors were also found to be independent factors for asthma control in the group adjusted for age and gender (Supplementary material 2A and B).

Table 2A. Clinical Characteristics of the High- and Low-adherence Groups.

	High adherence	Low adherence	p value
Patients (n)	177	113	
Male, n (%)	86 (48.6)	45 (40.2)	p=0.183
Age (years)	61.5±17.0	60.6±15.9	p=0.476
BMI (kg/m²)	22.9±3.3	23.0±4.4	p=0.830
Disease duration (years)	15.0±15.2	10.5±10.6	p=0.035
ICS duration (years)	7.6±6.7	7.0±6.7	p=0.309
Never smoker, n (%)	88 (49.7)	57 (50.9)	p=0.904
Handling error (%)	24.0±17.9	26.0±20.2	p=0.567
Total inhalation times (/day)	2.3±1.0	3.0±1.7	p<0.001

BMI: body mass index, ICS: inhaled corticosteroid. High adherence refers to the subjects with a modified adherence above the overall median (median: 33.3%). Low adherence refers to the subjects with a modified adherence below the median. Data are given as n (%) or means±standard deviation.

Table 2B. Clinical Characteristics of Low -and High-handling-error Groups.

	Low handling error	High handling error	p value
Patients (n)	153	137	
Male, n (%)	65 (42.5)	67 (48.9)	p=0.290
Age (years)	61.1±16.0	61.4±17.3	p=0.636
BMI (kg/m²)	23.1±4.0	22.8±3.5	p=0.173
Disease duration (years)	13.8±13.9	12.6±13.3	p=0.508
ICS duration (years)	7.9±6.7	7.8±6.8	p=0.565
Never smoker, n (%)	86 (54.2)	63 (46.0)	p=0.134
Modified adherence (%)	41.5±25.5	37.9±26.4	p=0.067
Total inhalation times (/day)	2.5±1.2	2.7±1.5	p=0.386

BMI: body mass index, ICS: inhaled corticosteroid. Low handling error refers to the subjects with handling errors less than the overall median (median: 20.0%). High handling error refers to the subjects with handling errors above the median. Data are given as n (%) or means±standard deviation.

Table 3. Clinical Characteristics among Different Inhaler Devices.

	Diskus®	Turbuhaler®	pMDI	p value
Patients (n)	171	84	32	
Male, n (%)	87 (50.9)	32 (38.1)	11 (34.4)	p=0.066
Age (years)	62.2±15.9	57.7±18.5	63.3±13.5	p=0.181
Disease duration (years)	14.3±15.1	12.2±12.1	11.0±10.0	p=0.429
Asthma Control Test	22.0±3.9	21.7±3.7	21.3±3.9	p=0.356
Exacerbation (%)	23.8	24.7	19.4	p=0.832
Modified adherence (%)	39.7±24.9[a]	43.7±30.1	30.1±13.8	p=0.007
Handling error (%)	25.7±19.6	22.5±17.1	26.1±19.2	p=0.479
Total inhalation times (/day)	1.9±0.4[b,c]	3.6±1.7[d]	2.9±1.5	p<0.001

a: p<0.01 between Diskus® and pMDI, b: p<0.001 between Diskus® and Turbuhaler®, c: p<0.001 between Diskus® and pMDI, d: p<0.05 between Turbuhaler® and pMDI.
Data are given as n (%) or means±standard deviation.

The median ACT score in this study was 23 points. In our previous study, the optimum cut-off point for predicting Global Initiative for Asthma (GINA)-defined asthma control was 23 points (17). It was therefore considered appropriate to divide the asthma control group in this study into uncontrolled and controlled subgroups, with 23 points as the threshold. We also set the ACT score cut-off to 20, which is the standard for poor control (Supplementary material 3), and confirmed that the trends between the two thresholds were similar.

Table 4A. Clinical Characteristics of Controlled and Uncontrolled Groups.

	Controlled	Uncontrolled	p value
Patients (n)	153	102	
Male, n (%)	70 (45.8)	49 (48.0)	p=0.798
Age (years)	61.6±15.5	59.3±18.9	p=0.542
BMI (kg/m^2)	23.2±3.3	23.1±4.0	p=0.569
Disease duration (years)	13.5±14.0	13.6±14.3	p=0.813
ICS duration (years)	7.6±7.0	7.5±6.5	p=0.787
Never smoker, n (%)	83 (54.2)	45 (44.1)	p=0.126
Modified adherence (%)	43.5±26.0	37.3±27.5	p=0.010
Handling error (%)	21.2±17.6	29.8±19.5	p<0.001
Total inhalation times (/day)	2.3±1.0	2.9±1.7	p=0.002

BMI: body mass index, ICS: inhaled corticosteroid. Controlled refers to the subjects with ACT scores above the median (median: 23). Uncontrolled refers to the subjects with ACT scores lower than the median. Data are given as n (%) or means±standard deviation.

Table 4B. Results of a Multivariate Logistic Regression Analysis for Controlled Asthma.

Variables	OR (95% CI)	p value
Modified adherence (over median)	1.77 (1.01–3.09)	p=0.046
Handling errors (below median)	2.19 (1.30–3.71)	p=0.003
Total number of inhalations (<2)	1.51 (0.80–2.86)	p=0.206

OR: odds ratio, CI: confidence interval

The univariate association between uncontrolled asthma (ACT score <23) and the rates of error in Diskus® and Turbuhaler® use are shown in Supplementary material 3A and B. For Diskus®, the rates of error in the following steps were significantly different between the controlled group and the uncontrolled group: inhale, stop breathing after inhaling, exhale, and repeat inhalation. For Turbuhaler®, the rates of error in confirming remaining doses and checking remaining doses were significantly different between the controlled and uncontrolled groups (Supplementary material 4A and B).

Discussion

In this study, we investigated both adherence to ICS treatment and ICS inhaler handling errors in the same patients. Our data indicate that both of these factors were independently associated with asthma control. Although this study was a retrospective design and the sample size was limited, it is the first to investigate adherence to ICS and device handling errors in the same population simultaneously.

One of the main objectives of this study was to investigate the relationship between adherence to ICS treatment and inhaler handling errors, and no significant correlation was found between these factors. In previous reports, low adherence to ICS treatment (18, 19) or the frequency of inhaler handling errors (14, 20, 21) correlated with worsening asthma control and exacerbation of symptoms. We believe that this study is important for showing that adherence to ICS and inhaler-handling errors are factors that are independently involved in asthma control, regardless of there being no direct correlation between them.

Recently, a consensus definition of adherence in respiratory medicine was reported (22). According to this definition, it is important to consider adherence separately in the various phases of initiation, implementation, and/or persistence. As a method of measuring adherence, canister prescription history and the required number of canisters calculated from the physician-issued prescriptions were used in this study. Since daily adherence to the prescriptions was not investigated, regular use of ICS could not be evaluated. However, the data used in this study were obtained from routine medical practice and were therefore considered meaningful for assessing current adherence.

The group with high adherence to ICS in this study was characterized by a long disease duration and less-frequent inhalation. It is well established that less-frequent inhalation is an important factor in increasing adherence (7, 16, 23). A relationship between ICS adherence and patient age has previously been described (24, 25), although no studies to date have reported an association between ICS adherence and disease duration. The long duration of asthma with age could improve disease understanding and result in increased adherence to ICS treatment. We divided our patients into two age groups using the age of 65 (defined as elderly) as the threshold (Supplementary material 5). Although the difference between the age groups was not significant (p=0.055), the elderly group tended to have better adherence, which was consistent with the findings of previous reports (24, 25).

In this study population, the use of devices was biased toward Diskus®, and the rates of Turbuhaler® and pMDI use were approximately 30% and 10%, respectively. Furthermore, ICS treatment adherence with Diskus® was significantly higher than that with pMDI (Table 3). However, no significant differences in handling errors were observed among the devices, in contrast to a previous report (12).

This discrepancy was believed to be due to the similarity in the age distribution between the groups and the many checkpoints in the device checklists (Supplementary material 3A and B).

Guidance for inhalation procedures can place significant demands on time and effort but is indispensable in ICS treatment. Furthermore, repeated instruction in inhalation procedures is often required in older patients. Dal Negro and Povero reported the cost per patient as the time spent by the nurse in explaining how to use the device to patients with asthma and chronic obstructive pulmonary disease (COPD) (26). We did not investigate differences in difficulty with acceptance and handling among the devices in the questionnaire. Devices with reduced handling procedures are generally considered suitable for prescription to older patients (27). However, devices differ in terms of the handling complexity, so the choice of device should be considered when prescribing such a device to older patients.

In this study, the mean rate of adherence to ICS was significantly lower than the rate observed in our previous study (approximately 80%) (15, 16). Although differences in prescribing physicians and medical institutions may have had an impact, the current data were obtained only from the patients and their pharmacists. Therefore, the data do not include information such as the medical institutions that the patients visited, asthma control evaluated by the physicians, disease severity, and history of exacerbation. Without such information, it is difficult to explore the factors that would explain why the adherence was unexpectedly low, although in clinical settings, it may actually be this low. One reason that drug adherence was low in this study might be the characteristics of the devices. For inhaler devices without accurate counters, such as pMDI or Turbuhaler®, the patient tends to inhale more puffs than the proper count of inhalers, so the reported adherence may be lower than the actual adherence. The other reason for low drug adherence might be the increased proportion of ICS with a LABA. In our previous study, ICS was a single agent; however, approximately 70% of ICS in the present study was in combination with a LABA. Due to the high efficacy of this combination (28), its usage controls asthma very well, possibly leading to interruptions in regular treatments. Conversely, it can be said that even in clinical practice, it is possible not only to suppress exacerbation but also to improve the quality of life further by firmly maintaining adherence.

In summary, we investigated both adherence to ICS and ICS inhalation device handling errors in the same patient population and found that modified adherence was extremely low, at only 39.5%. Total number of inhalations correlated with adjusted adherence to ICS treatment. Adherence to treatment and device handling errors were independent factors contributing to the ACT scores, based on a multivariate analysis. Our data indicate that adherence to ICS treatment and device-handling errors are important factors to address in order to achieve better asthma control.

The authors state that they have no Conflict of Interest (COI).

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