Which inhaled corticosteroid and long-acting $\beta$-agonist combination is better in patients with moderate-to-severe asthma, a dry powder inhaler or a pressurized metered-dose inhaler?

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**ABSTRACT**

Two main types of devices are used to facilitate the administration of inhaled corticosteroid (ICS) and long-acting $\beta$-agonist (LABA) in combination, dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). There are few reports comparing the effects of the two devices, and it is unknown which should be recommended for asthma patients with given sets of characteristics. In the current study, the beneficial effects and side effects associated with DPIs and pMDIs were compared, and the question of which device should be recommended for asthma patients was investigated. A prospective, randomized, crossover, comparative study in adult outpatients with asthma was conducted using salmeterol/fluticasone propionate combination (SFC) 50 $\mu$g/250 $\mu$g, one inhalation of Adoair Diskus 125 Aerosol twice daily, for 8 weeks. Questionnaires, exhaled nitric oxide (FeNO) tests and pulmonary function tests were administered after the use of each device for 8 weeks, and the results derived from each device were compared. Sixty-eight subjects were included in the final analysis. There were no significant differences between quality-of-life scores, FeNO, spirometry test results and forced oscillation results. With regard to patient preferences, 57.4% preferred the Adoair Aerosol and 35.3% preferred the Adoair Diskus, as determined via the comparative evaluation questionnaire. Although DPI prescription accounts for the predominant market share of combined ICS/LABA in Japan, patients preferred a pMDI device to a DPI device. Compared to DPIs, pMDIs may be the preferential choice for patients with asthma.

**Introduction**

In the Global Initiative for Asthma (GINA) report (Global Initiative for Asthma, 2017), the preferred controller of choice is inhaled corticosteroid (ICS) and long-acting $\beta$-agonist (LABA) combination for treatment step 3 or above. The availability of different ICS/LABA medication combinations and administration devices varies from country to country, and such devices include dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). DPIs are considered easier to use (Virchow et al., 2008). These devices also have limitations however, such as dependency of drug particle size on flow rate and loss of the metered dose if the patient exhales through the device before inhaling (Virchow et al., 2008). A relatively recent increase in the number of different types of inhaler devices available has resulted in a confusing number of choices for clinicians who are responsible for selecting delivery devices for individual patients (Dolovich et al., 2005).

Five types of devices and four ICS/LABA combinations are currently available in Japan, and only salmeterol/fluticasone propionate combination (SFC) is available in both DPI and pMDI devices. However, the differences in the beneficial effects and side effects between these two types of medications and the differences in patients’ preferences have not been elucidated, and it is unknown which device should be recommended for asthma patients with given sets of characteristics.

In the current prospective, randomized, crossover study, SFC DPIs and SFC pMDIs administering the same components and doses were compared in adult outpatients with asthma. The beneficial effects, side effects and patient preferences associated with the two devices were analyzed and compared in conjunction with various patient characteristics. A primary aim of the study was to shed some light on which devices should be recommended for asthma patients with specific sets of characteristics.
Methods

Seventy-two outpatients aged ≥20 years with moderate-to-severe asthma who had been attending the Department of Respiratory Medicine and Allergology at Kindai University Nara Hospital (Ikomaji, Japan) and who required treatment with a medium-dose ICS/LABA combination were initially enrolled in the study. Informed consent was obtained from all subjects, and the exclusion criteria were as follows: inability to inhale unassisted; inability to perform spirometry tests; pregnancy; severe comorbidities affecting quality of life (QoL) such as malignancy, cardiac failure, renal failure or severe liver dysfunction; and current smoker status. Subjects were randomly assigned to a ‘DPI preceding’ group (i.e. DPI first, then pMDI) or a ‘pMDI preceding’ group (pMDI first, then DPI), and their background characteristics were investigated (Supplementary Figure 1). The SFC (Adoair®, GlaxoSmithKline, Tokyo, Japan) regimens were inhalation of 1 blister (50 μg/250 μg) twice daily for the DPI (Adoair® Diskus®) and inhalation of 2 puffs (50 μg/250 μg) twice daily for the pMDI (Adoair® 125 Aerosol). No subject used a spacer such as AeroChamber® for pMDI prior to the enrollment and no spacers were used for pMDI in this study.

The following evaluation items were investigated after the use of each device for 8 weeks: the Asthma Control Test (ACT) Questionnaire (Schatz et al., 2009; Thomas et al., 2009; Global Initiative for Asthma, 2017); the Asthma Health Questionnaire (AHQ)-33-Japan (Arioka et al., 2005; Muraki et al., 2008; Ichinose et al., 2017; Tohda et al., 2017); the original questionnaire for handling, side effects, adherence and overall evaluation (Supplementary Table 1); physical findings; fractional exhaled nitric oxide (FeNO) using NIOX MINO® (Chest M.I., Tokyo, Japan) (Harnan et al., 2015); spirometry using a Chestac-33 (Chest M.I., Tokyo, Japan); and respiratory system resistance and reactance as determined via the forced oscillation technique (FOT) using MostGraph-01® (Chest M.I., Tokyo, Japan) (Abe et al., 2016; Shirai and Kurosawa, 2016).

When exacerbation due to a common cold or a similar cause overlapped with the visit date, the evaluation appointment was postponed for up to 4 weeks. The examinations were performed from 9 a.m. to 11 a.m., and 2–4 hours after the patients took their normal morning medications (SFC and all other morning medications). Use of short-acting β-agonist (SABA) within 12 hours of the visit was prohibited. Changes in concomitant medications were also prohibited from 8 weeks before the examination and throughout the study period. On the final day of the study, a questionnaire survey (Supplementary Table 2) to compare the SFC-DPI and SFC-pMDI was also administered. The study protocol was approved by the Institutional Review Board at Kindai University Nara Hospital and was implemented in compliance with the Declaration of Helsinki.

Statistical analysis

Data are presented as the mean ± standard deviation. Statistical differences were assessed via the paired t-test for comparison between the two groups with correspondence, Student’s t-test for comparison between independent groups and Pearson’s goodness-of-fit test for comparison between categorical variables represented by a contingency table. With regard to device selection, odds ratio and confidence interval were calculated via logistic regression. Statistical analyses were performed using JMP® version 10.0.2 statistical software (SAS Institute Japan, Tokyo, Japan), and p < .05 was considered statistically significant.

Results

Seventy-two subjects were initially enrolled, and four of these subsequently dropped out – two who did not go to hospital on the final day of DPI administration in the pMDI preceding group, and one who revoked their consent and one who discontinued due to discomfort in the throat while using the pMDI in the DPI preceding group (Supplementary Figure 1). In the remaining 68 subjects, there was no overlap between the survey date and exacerbation due to a common cold or a similar cause, and all of them were able to take SFC during each of the 8-week periods. However, in 4 of the 68 subjects, FeNO could not be measured due to a technical problem. The characteristics of the 68 subjects included in the final analysis are shown in Table 1. In the final analysis, the DPI preceding group included 35 subjects and the pMDI preceding group included 33. Thirty-eight percent of the subjects had a history of smoking, and 57% had combined allergic rhinitis. The average ACT score was 22.8, and asthma was mostly well controlled as indicated by scores of ≥20 in 59 subjects (86.8%) and ≤19 in 9 subjects (13.2%). The mean grip strength of the fingers between the thumb and the forefinger and middle finger using a pinch meter was 7.0 kg, and all subjects could press a pMDI in order to self-administer a puff. Peak inspiratory flow (PIF) using the In-Check® (Matsuyoshi & Co., Ltd., Tokyo, Japan) with an adapter for Diskus® resistance (A/A/D) was higher than 30 L/min as a minimum of optimum PIF (van der Palen, 2003; Kawamatawong et al., 2017), except in one subject (29 L/min). All subjects have been using medium-dose ICS, and there were more DPI users than pMDI users (n = 45 for DPI, n = 20 for pMDI and n = 3 for both devices).

Vital signs, FeNO levels and QoL scores (ACT and AHQ-33-Japan) after using the DPI or the pMDI for 8 weeks each are shown in Table 2. There were no significant differences in vital signs, FeNO levels or QoL scores between the DPI and pMDI datasets. An original questionnaire was also administered at the end of administration with each inhalation device (Table 3). Items 1 and 2 relate to handling and the inhalation process, the contents of the corresponding questions differ, and they were not a validated aspect of the comparison. Therefore, the differences between these items were not analyzed. With regard to items 4 and 5 however, the DPI seemed easier (item 4, p < .1; item 5, p = .0005). In side effect items, DPI was worse with respect to hoarseness (item 6), but this difference was not statistically significant. There were no significant differences between the results pertaining to any of the other items. In pulmonary function tests, there were no significant differences in spirometry parameters or MostGraph-01® parameters (Table 4). There were also no
At the end of the study, a questionnaire comparing the DPI and the pMDI was administered (Figures 1 and 2). With expiratory, inspiratory and expiratory minus inspiratory parameters at MostGraph-01®️, the proportion of previous pMDI users who nominated the pMDI device was 53.3% (24 subjects, 18 subjects for DPI better and 3 subjects for equivalent), and the proportion of previous DPI users who nominated the pMDI device was 65% (13 subjects, 5 subjects for DPI better and 2 for equivalent), and this difference was not statistically significant ($p = .2709$).

### Discussion

Even though inhalation therapy is a cornerstone in asthma and chronic obstructive pulmonary disease management, little advice is available in the relevant guidelines relating to inhaler selection. A relatively recent increase in the number of different inhaler devices available has resulted in a confusing number of choices for clinicians who are responsible for selecting delivery devices for individual patients (Dolovich et al., 2005). Two main types of devices are available for the

#### Table 1. Patient characteristics.

| N       | 68          | Pulmonary function test |
|---------|-------------|-------------------------|
| Male/female | 32/36       | IC (L)                  |
|          |             | FVC (L)                 |
|          |             | %FEV (%), P < .05       |
|          |             | FEV1 (L)                |
|          |             | %FEV1 (%)               |
|          |             | Post-BD FEV1 (L)        |
|          |             | %Post-BD FEV1 (%)       |
|          |             | Previous medications   |
|          |             | ICS/LABA                |
|          |             | SFC (DPI)               |
|          |             | SFC (pMDI)              |
|          |             | FBC                     |
|          |             | CIC + Sal               |
|          |             | Mo                      |
|          |             | FP                      |
|          |             | Other                   |
|          |             | Both                    |

#### Table 2. Vital signs, FeNO levels and QoL scores (ACT and AHQ-33-Japan) after using the DPI or the pMDI.

|                      | Adoair®️ Diskus®️ | Adoair®️ Aerosol | p-Value |
|----------------------|-------------------|-----------------|---------|
| Systolic BP (mmHg)   | 129.6 ± 17.2      | 130.3 ± 16.7    | .3407   |
| Diastolic BP (mmHg)  | 76.8 ± 9.6        | 77.1 ± 9.6      | .3655   |
| Pulse rate (/min)    | 79.5 ± 11.3       | 78.1 ± 11.4     | .1190   |
| FeNO (ppb)           | 28.9 ± 19.6       | 29.9 ± 25.4     | .3304   |
| ACT                  | 22.8 ± 2.7 (median) | 22.9 ± 2.4   | .2857   |
| Concomitant          | LTRA              | TEO             | 4       |
| Device type          | pMDI              | DPI             | 45      |
| Pinch meter (kg)     | 7.0 ± 2.1         | 7.0 ± 2.1       | .1383   |
| PIF (adaptor-free, L/min) | 216.9 ± 77.7   | 216.9 ± 77.7  | .0822   |
| (A/A/D, L/min)       | 92.3 ± 26.2       | 92.3 ± 26.2     | .1933   |

FeNO: fractional exhaled nitric oxide; QoL: quality of life; ACT: Asthma Control Test; A/A/D: adapter for Diskus®️ resistance; PIF: peak inspiratory flow; IC: inspiratory capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; BD: bronchodilator; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; SFC: salmeterol/fluticasone combination; DPI: dry powder inhaler; pMDI: pressurized metered-dose inhaler; FBC: formoterol/budesonide combination (DPI); CIC: ciclesonide (pMDI); Sal: salmeterol (DPI); Mo: mometasone (DPI); FP: fluticasone propionate (DPI); LTRA: leukotriene receptor antagonists; TEO: theophylline.
In the present study, the DPI was also associated with better overall evaluation more subjects reported that they preferred the pMDI. Although the reason why more subjects preferred the pMDI could not be elucidated, it was evidently not simply that a new device was preferred, because the ratio of previous DPI users who nominated the pMDI device was less than that associated with the DPI. The number of subjects who reported that the pMDI was more effective than the DPI was higher than the number of subjects who reported the reverse, despite the fact that there were no significant differences in FeNO levels or any of the pulmonary function parameters tested. In addition, in the overall evaluation more subjects reported that they preferred the pMDI. Although the reason why more subjects preferred the pMDI could not be elucidated, it was evidently not simply that a new device was preferred, because the ratio of previous DPI users who nominated the pMDI device was less than the ratio of previous pMDI users who nominated pMDI device.

Inhaler devices may influence patient compliance with long-term asthma medication regimens (Darbà et al., 2016). pMDI devices such as those used for ICS/LABA initial treatment are associated with longer treatment persistence and better treatment adherence in asthma, as well as lower exacerbation rates, reduced use of health resources and lower costs (Sicras et al., 2016). We studied pMDIs without a spacer in the present study. However, pMDIs without a spacer in the present study. However, pMDIs were more effective—especially in elderly patients—than the DPI, although the difference was not statistically significant. In the final comparative questionnaire, pharyngolaryngeal side effects including hoarseness were also more strongly associated with the DPI than the pMDI. The number of subjects who reported that the pMDI was more effective than the DPI was higher than the number of subjects who reported the reverse, despite the fact that there were no significant differences in FeNO levels or any of the pulmonary function parameters tested. In addition, in the overall evaluation more subjects reported that they preferred the pMDI. Although the reason why more subjects preferred the pMDI could not be elucidated, it was evidently not simply that a new device was preferred, because the ratio of previous DPI users who nominated the pMDI device was less than the ratio of previous pMDI users who nominated pMDI device.
inhalation than for DPI in post-elementary school-aged patients (Miyahara et al., 2008). Notably however, according to individual patients, the additional use of a spacer may hinder adherence. Therefore, it is necessary to consider the characteristics and needs of individual patients.

The characteristics of patients who preferred DPI and those who preferred pMDI were compared, but no significant differences were detected. The pMDI is still the most frequently prescribed device worldwide, but even after repeated tuition many patients fail to use it correctly (Virchow et al., 2008). Notably, the device market share in Japan is dominated by the DPI. The current Japanese ICS/LABA combination is predominantly accounted for by the DPI, and the numbers of prescriptions for outpatients are 14,015,551 (equating to 78.155 billion yen) for the DPI and 1,244,337 (equating to 6.494 billion yen) for the pMDI (AnswersNews, http://answers.ten-navi.com/pharmanews/7962). We cannot fully explain the reason DPI dominates the market share in Japan. However, in part it may be related to the lower malfunction rate and shorter instruction time necessary for a DPI. In addition, the preferences of medical professionals may be different than those of patients.

A limitation of the present study is that the device used for rapid relief with rescue SABA inhalers, DPI or pMDI, was not regulated in the present study, which may have influenced subject preference. In addition, the subjects in this study all had severe asthma requiring medium-dose ICS/LABA, so our findings may not be applicable to patients with different severities of asthma.

The current study investigated patients’ preferences with regard to SFC (Adoair®,) DPIs and pMDIs. Despite the current Japanese market share distribution, patients with asthma tended to prefer the pMDI to the DPI. Therefore, prescribing the pMDI may be preferable, considering patients’ preferences. Further investigation of the selection of the DPI or the pMDI for individual patients is necessary in the future.

**Disclosure statement**

The authors report no declaration of interest.
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