The Clinical Evaluation of the Acceptance of Fluticasone Propionate Diskus® by Older Japanese Patients with Bronchial Asthma

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ABSTRACT
Background: Fluticasone propionate (FP) Diskus® is generally regarded as an easy to use and efficacious inhaled device. This study clinically evaluated whether its easy handling and inhalation process were affected by the aging factor or not, compared with those of the FP Diskhaler® and Beclomethasone dipropionate (BDP).
Methods: Twenty-four elderly patients with stable moderate asthma (12 aged 65–74 years and 12 aged 75 years or older) who were accustomed to using the Diskhaler® were evaluated by measuring the required time for finishing one-time inhalation with the device, compared with 7 patients aged less than 65. Ten elderly patients (5 aged 65–74 years, and 5 aged 75 years or older), who used the BDP, were also similarly evaluated and compared with 8 patients aged less than 65. All subjects then switched to use with the Diskus® and the required time for finishing one-time inhalation was measured soon after and 2 weeks after the change. The patients’ usage impressions were also questioned.
Results: The mean required times (seconds) were significantly different between patients aged 75 years or older, and with patients less than 65 years of age: 45.8 ± 8.1 vs. 31.8 ± 12.3 (p = 0.046) in the BDP group, and 56.8 ± 25.3 vs. 33.3 ± 18.5 (p = 0.047) in the Diskhaler®, respectively. Soon after changing to the Diskus®, those times became insignificant in both groups. After 2 weeks, the required time for using the Diskus® was significantly shortened in all age groups. 50.0% patients in the BDP group and 79.2% in the Diskhaler® group finally chose the Diskus®.
Conclusions: The FP Diskus® inhalation was not affected by the aging factor and all patients could quickly get accustomed to using it, suggesting its clinical efficacy for older patients.

KEY WORDS
asthma, drug compliance, Fluticasone propionate Diskus®, older patients

INTRODUCTION
Steroid inhalation, as recommended in the Japanese guideline for bronchial asthma1 and the Global Initiative for asthma (GINA) 2002,2 currently plays a pivotal role in daily asthma therapy. Early and effective therapy with inhaled corticosteroids results in long-term remission in the majority of asthmatic patients.3 Many effective inhaled corticosteroids and associated specialized delivery device systems have been developed and are clinically distributed world-wide at present. There has been an abundant accumulation of clinical evidence showing the therapeutic efficacy of the new dry powder type inhaled corticosteroids.4–7 However, I think, the clinical evaluation of the patients’ view of usage has been insufficient; in particular for aged patients. The most distinguishing clinical factor in elderly patients compared to young and middle-aged patients is aging itself. This factor often strongly affects the introduction and continuation of inhaled corticosteroids for older patients. The aging changes, such as the decline of understanding, eye-
and also evaluated the acceptance of the FP Diskus changing of BUD-TH, the change to the FP Diskus regarded as easy and efficacious, has frequently been haled corticosteroid and a device which is generally InspirEase methasone dipropionate (BDP) with a spacer device

In this study, we showed that what was generally considered to be easy for young and middle-aged patients was not always easy to handle for aged patients, suggesting the major influence of the aging factor upon the daily use of an inhalation device.

FP Diskus®, another new type of dry powder inhaled corticosteroid and a device which is generally regarded as easy and efficacious, has frequently been used in recent daily clinical fields. In addition to the changing of BUD-TH, the change to the FP Diskus® from other types of inhaled corticosteroids also often occurs for various therapeutic reasons, requiring the same kind of clinical evaluation. This study clinically investigated whether the easy handling of the FP Diskus® will be affected by the aging factor or not, and also evaluated the acceptance of the FP Diskus® by older Japanese patients with bronchial asthma, when changed from the previously distributed inhaled corticosteroids, BDP with a spacer device InspirEase® and the FP Diskhaler®.

METHODS

PATIENT CHARACTERISTICS

Before enrollment in the study, the clinical meaning, purpose of this study, and the possible disadvantages including side effects caused by changing to the new inhaled corticosteroids, were explained in detail to each patient. Subsequently, 34 elderly Japanese patients aged 65 or older and 15 aged less than 65 with stable moderate bronchial asthma (Step 2–3 according to Japanese guidelines for the diagnosis and management of bronchial asthma),¹ who could fully understand this study and who showed their intention to join this study, were the subject of this study. They consisted of 24 older asthmatic patients (12 aged 65–74 years and 12 aged 75 years or older) and 7 patients aged less than 65 who had become accustomed to using the Diskhaler®, and 10 older patients (5 aged 65–74 years and 5 aged 75 years or older) and 8 patients aged less than 65 who had become accustomed to inhaling the BDP with InspirEase®. All subjects had used their inhaled corticosteroids daily for at least more than 6 months with a stable asthmatic condition. Patient characteristics are shown in Table 1. This study was carried out in accordance with the principles embodied in the Helsinki Declaration of 1995 (as revised in Edinburgh 2000). Before starting this study, written informed consent for study participation was obtained from all the enrolled patients.

### Table 1 Patients Characteristics

<table>
<thead>
<tr>
<th>Age range</th>
<th>older patients</th>
<th>young and middle-aged patients</th>
<th>the BDP group</th>
<th>the FP Diskhaler group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>65–74</td>
<td>75–</td>
<td>Total</td>
</tr>
<tr>
<td>Numbers of Patients</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
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<td>Mean age (yr)</td>
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<td>69.1 ± 3.2</td>
<td>79.3 ± 3.8</td>
<td>74.8 ± 4.4</td>
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<td>3/2</td>
<td>4/1</td>
<td>6/2</td>
</tr>
<tr>
<td>Type of asthma (Atopic/Non-atopic)</td>
<td>2/8</td>
<td>2/3</td>
<td>0/5</td>
<td>7/1</td>
</tr>
</tbody>
</table>

PROTOCOL

All of the patients in the BDP group used 800 μg/day of BDP daily and were changed to a half dose of FP Diskus® in this study. All patients in the FP Diskhaler® group used 400 μg/day of FP Diskhaler® daily and were changed to the same dose as above of FP Diskus® in this study. Finally, both groups were evaluated according to the following terms.

Measurement of Frequency of Explanation Required at the Introduction of This Device

Before changing to the new device, FP Diskus®, each patient was carefully instructed on how to use the device and we investigated the frequency of explanation needed at the time of the introduction until each of them could fully understand this inhalation method and perfectly independently perform the successive inhalation process. After 2 weeks we confirmed whether all of subjects in this study could perform inhalation correctly. Each subject was checked on the detailed inhalation process of the FP Diskus®.
Comparison of Duration of Time Required for Completing an Inhalation by Each Inhaled Device

The required time for finishing one-time inhalation with each inhalation device was measured before, the same day soon after finishing the introductive explanation of the FP Diskus®, and 2 weeks after changing to the FP Diskus®. The required times for finishing one inhalation with BDP was defined as the time from just starting to set the spacer device InspirEase® according to the starting sign, to the time finishing one inhalation, just before starting the next expiratory breath. The required time for finishing one inhalation with the FP Diskhaler® was defined as the time from starting to set a sheet of Rotadisk® according to the starting sign to the time finishing one inhalation, just before starting the next expiratory breath. The time with the FP Diskus® was also defined as the time from starting to slide the cover according to the starting sign, to the time to finish one inhalation, just before starting the next expiratory breath. Each required time was measured three times and then we calculated the average. In addition, the required times were measured by the same doctor throughout this study.

Patients’ Questionnaires Concerning Their Acceptance and Impressions of the FP Diskus®

The following simple patient questionnaires, which were easy even for aged patients to answer, concerning their impressions of using the FP Diskus®, were given after 2 weeks.

Q1: Do you feel it is easy or not easy to use the FP Diskus® daily, compared with your previous device?

Q2: Which do you wish to continue to use, the FP Diskus® or your previous device?

Q3: If you notice anything when you use the FP Diskus® for these 2 weeks, please let me know.

Side Effects

The author questioned all of the patients in detail for the occurrence of side effects during the 2 weeks after changing to the FP Diskus® or not.

Comparison of Drug Compliance after 8 Weeks

Using each patient’s asthma diary and the number on the counter of FP Diskus®, drug compliance was also investigated and compared 8 weeks before and after changing to the FP Diskus®.

Comparison of Daily Peak Expiratory Flow (PEF) and Pulmonary Function Test

8 weeks after the start, the improvement of daily peak expiratory flow (PEF) checked in accordance with each patient’s asthma diary and pulmonary function tests was also measured.

STATISTICAL ANALYSIS

All data are expressed as mean ± standard deviation. Each comparison in Figure 2 and Figure 3 was made using the unpaired student t test and each compari-
Fig. 2 The comparison of the required inhalation time among each age range groups in the BDP group (A) and the FP Diskhaler® group (B). Statistical significance: *P < 0.05. N.S. represented as no statistical significance compared with the time of patient group aged less than 65.

Fig. 3 The comparison of the required inhalation time soon after changing to the Diskus® in the pre-BDP group (A) and the pre-FP Diskhaler® group (B). N.S. represented as no statistical significance compared with the time of patient group aged less than 65.

son in Figure 4 was done by using the paired student t test. P values of less than 0.05 were considered significant.

RESULTS
Patients in both groups tolerated the new medication well and no unexpected adverse events were happened during this study.

MEASUREMENT OF FREQUENCY OF EXPLANATION REQUIRED AT THE INTRODUCTION OF THIS DEVICE (Fig. 1)
As shown in Figure 1, within the age range of 65–74 years old, 2 patients (40.0%) in the BDP group and 3 patients (25.0%) in the FP Diskhaler® group required more than 2 explanations, until they could fully understood this inhalation method and perfectly performed the successive inhaled process by themselves. However, no more than a total of 3 explanations in both groups were required. In addition, 2 patients (40.0%) aged 75 years and older in the BDP group, required 2 explanations and 3 explanations respectively at the introduction of FP Diskhaler®, 6 patients (3 (25.0%) and 3 (25.0%)) in the FP Diskhaler® group needed 2 and 3 explanations, respectively. In contrast, all young and middle-aged patients could adequately understand and perfectly perform the successive inhaled process of FP Diskus® after only one careful explanation at the introduction.

After 2 weeks, we confirmed in detail whether all the patients in this study could properly perform the inhalation method or not. There were no serious mis-
takes, which affected the successive inhaled process itself, in either group. However, 9 older patients (26.5%) (4 patients in the BDP group and 5 in the FP Diskhaler® group) were found to unnecessarily return the lever after an inhalation. Furthermore, 3 older patients (8.8%) (these 3 patients were all in the BDP group) took a breath while attaching the device to the mouth. Even in the young and middle-aged group, 2 patients (13.3%) (1 patient in the BDP group and 1 in the FP Diskhaler® group) also unnecessarily returned the lever after an inhalation. Those minor mistakes could be easily corrected at that time. At the end of this study, all older patients enrolled in the study, as well as young and middle-aged patients, could use the Diskus® smoothly.

MEASUREMENT OF THE TIME REQUIRED FOR COMPLETING AN INHALATION BY EACH INHALATION DEVICE (Figs. 2-4)
As shown in Figures 2 (A) and (B), there were the significant differences in the required inhalation time between patients aged less than 65 and ones aged 75 and over, in the BDP group ($p = 0.046$) and the FP Diskhaler® group ($p = 0.047$), respectively. On the other hand, soon after changing to the Diskus®, these significant differences disappeared in the pre-BDP group ($p = 0.053$)(Fig. 3(A)), and in the pre-FP Diskhaler® group ($p = 0.051$)(Fig. 3(B)). Furthermore, after 2 weeks, the required time with the Diskus® was significantly shortened in the patient group aged 75 and over in the pre-BDP group (Fig. 4 (A)). Furthermore, the required inhalation time in any age range of patients in the pre-FP Diskhaler® group were significantly shortened after 2 weeks, compared with the time soon after introduction (Fig. 4(B)).

RESULTS OF THE PATIENT QUESTIONNAIRES
Results of the patient questionnaires after 2 weeks are shown as follows.

Q1: Do you feel it is easy or not easy to use FP Diskus® daily, compared with your previous device?
80.0% of older patients in the BDP group and 91.7% in the FP Diskhaler® group answered that the handle of FP Diskus® was easier compared with their previous inhalation device. The rest of the subjects responded that the difficulty in handling of the FP Diskus® was almost the same compared with their previously used devices. In contrast, all of young and middle-aged patients answered that FP Diskus® was so much easier to use, compared with their previous device.

Q2: Which do you wish to continue to use, FP Diskus® or your previous device?
50.0% of aged patients chose to continue FP Diskus® inhalation in the BDP group, while 30% chose the previously used BDP and 20% answered that any device will do. On the other hand, 79.2% of aged patients in the FP Diskhaler® group finally chose to continue FP Diskus® inhalation, while 12.5% chose the previously used device and the rest answered that any will do. In contrast, all in the young and middle-aged group finally chose FP Diskus®.

Q3: If you notice anything when you use FP Diskus® for these 2 weeks, please let me know
5 patients answered that the counter system in FP Diskus®, which decreased the number one by one per inhalation, was so convenient due to the fact that they could confirm whether they had actually finished their daily inhalations. However, 3 of the patients pointed out that the size of counter number was too small for aged patients with presbyopia and should be made bigger.
Fig. 5  The comparison of drug compliance between 8 weeks before and after changing to the FP Diskus®.

SIDES EFFECTS
A hoarse voice and abnormal dry feeling in the mouth after FP Diskus® inhalation occurred in 11 patients out of the 34 patients (32.4%) as side effects, but in none of the young and middle-aged patients. However, each side effect was so mild that they did not need to discontinue use of the FP Diskus® inhalation. Most of the side effects were diminished or disappeared by gargling soon after one inhalation or by controlling each patient’s inhalation speed.

RESULT OF DAILY DRUG COMPLIANCE (Fig. 5)
Drug compliance was also investigated 8 weeks before and after changing to the FP Diskus®, 8 weeks before changing to the FP Diskus®, 7 elderly patients in the BDP group (3 patients aged 65–74 years and 4 ones aged 75 years or older) and 17 in the FP Diskhaler® group (7 patients aged 65–74 years and 10 ones aged 75 years or older) had some inconsistency between the daily inhalation times as noted in their asthma diary and the actual residual doses of inhaled corticosteroids. However, 8 weeks after changing to the FP Diskus®, almost all the older patients’ daily drug compliance had improved (Fig. 5). The sum of the daily regular inhalation times in patient’s asthma diary were almost the same as the number indicated on the counter of the Diskus®, suggesting good daily drug compliance.

RESULTS OF CHANGES IN DAILY PEF AND PULMONARY FUNCTION TEST
As for daily PEF, there was no statistical significance found between before changing to the FP Diskus® and 8 weeks after changing to the FP Diskus® in both groups in this study. In the BDP group, the mean PEF values (L/min) of the patients aged 75 years or older, 65–74 years, and less than 65 years old were 279.0 ± 112.2 vs. 281.6 ± 112.7, 281.7 ± 86.3 vs. 282.2 ± 92.4, and 441.0 ± 49.0 vs. 449.6 ± 54.0, before and after changing to FP Diskus®, respectively. On the other hand, those (L/min) in the Diskhaler® group were 224.6 ± 105.1 vs. 225.5 ± 107.3, 302.5 ± 81.5 vs. 302.1 ± 82.2, and 394.4 ± 121.7 vs. 392.3 ± 119.9, before and after changing to the FP Diskus®, respectively. As for the pulmonary function test, there was also no statistical significance found between before changing to the FP Diskus® and 8 weeks after changing to FP Diskus® in both groups in this study (data not shown).

DISCUSSION
In order to directly send inhaled corticosteroids into the asthmatic inflammatory airways and to display its therapeutic effects fully, an inhalation device plays a pivotal role in inhaled corticosteroid therapy. Many inhalation devices have been developed and are used in the present daily clinical field, and most of them may tend to focus upon how much drug can be delivered effectively into airways as possible. Even though the inhaled corticosteroid itself has a powerful effect upon asthmatic inflammation and its delivery is very good, patient training and compliance will continue to be important factors in the success, or failure, of inhaled therapy. Moreover, the patient’s poor acceptance of the device possibly causes insufficient inhalation, spoiling its therapeutic usefulness. As shown in our previous study, although a patient’s poor inhalation technique and poor acceptance of the
device can be caused by various individual reasons, the aging factor, including cognitive function, often has a remarkable effect upon its therapeutic usefulness. What is generally easy for young and middle-aged patients to handle is not always easy for older patients. The aging factor strongly influences both the smoothness in handling the device and the ease of getting accustomed to it, which are closely related to the required inhalation time.

In this study, by means of measuring the required inhalation time comparing young and middle-aged patients, the author showed that the inhalation time with the Diskus® was not strongly affected by the aging factor, compared with the other two devices BDP with a spacer device InspirEase® and FP Diskhaler®. Generally, when there are many processes in handling the device leading to one complete inhalation, it will, of course, take longer to finish the inhalation process. Although times vary with each inhaled devices, the relatively longer required inhalation time does not detract from the therapeutic benefit to the patients. The comparison of the required inhalation time among different devices themselves is not of any direct significance, but also the shorter inhalation time does not always signify the clinical superiority of the device. However, the comparison of the required inhalation times using the same device is another story. When it takes a significantly longer time for older patients to finish the inhalation process with the device, compared to that of young and middle-aged patients when using the same device, important clinical meaning is highlighted, particularly in that difficult and time-wasting handling for older patients within the course of inhalation process with this device exists actually requires a therapeutic approach. As the aim of this study is to make it clear that for older patients there is a difficulty handling the device due to the aging factor, the comparison of the required inhalation time when using the same device between older patients and young and middle-aged ones is clinically important. And, as another therapeutic aim is to correct the wrong handling which disturbed the daily smooth inhalation and to acquire a comfortable process for older patients, the time-course comparison when using the same device will be also important to evaluate how the patients got accustomed to handling this device.

As shown in this study (Figs. 2(A), (B)), despite the fact that the patients who were the subject of this study had already been using their devices more than 6 months, there were significant differences in the required inhaled time, for using both the BDP with InspirEase® and the FP Diskhaler®, between young and middle-aged patients and older ones, in particular those aged 75 and more, suggesting the existence of difficult and time-wasting handling in the inhalation process with the BDP and the FP Diskhaler® for older patients. In contrast, soon after changing from these previously used devices to the Diskus®, those significant differences, in the inhalation time between young and middle-aged patients and older patients, disappeared (Figs. 3(A), (B)), meaning there was less time-wasted and a less complicated handling process when using the Diskus®, for older patients. Furthermore, all the patients in this study, older as well as the young and middle-aged ones, learned the use of FP Diskus® correctly and performed its handling smoothly by the end of the 2 week-long study, which was accompanied by significant reductions in the required inhalation time (Figs. 4(A), (B)). This suggests it is easy to get accustomed to handling the device. A previous study by Boulet et al. reported that 84% of 376 subjects (age range:12–75 years) could use the Diskus® after the first explanation, while 73% did in the Diskhaler® group, and they also reported that patients preferred Diskus® to Diskhaler® (73% vs. 15%). Their data is not inconsistent with the results of this study.

Moreover, all in the young and middle-aged group answered that handling the FP Diskus® was easy and also finally chose the FP Diskus®. In contrast, despite more than 80% of older patients in this study answering that the handling of the FP Diskus® was easier compared with their previous inhalation devices, 50.0% of aged patients in the BDP group and 79.2% of those in the FP Diskhaler® group finally chose to continue FP Diskus® inhalation, while the rest did not, suggesting the possibility of the existence of another clinically influenced factor such as devotion to the previous device because they have already gotten accustomed to its handling.

In this study, the author also showed that the daily drug compliance of most patients improved after changing from a previously used device to FP Diskus® (Fig. 5). The enhancement of patient drug compliance in this study may be partly due to the ease of getting accustomed to handling the device, and partly to the counter system which decreases the number one by one per inhalation. Each patient can know the exact number of doses left and can confirm, whether he has already taken the daily dose, by the indicated number on the counter. This offers the elderly patients’ relief, thereby ensuring good compliance. Furthermore, the counter system is also convenient for the physician as s/he confirm whether the patient is regularly using the inhaled drug or not according to his therapeutic plan, by checking the counter number on the device which the patients bring into the clinic. However, as some patients actually pointed out, the size of counter number is too small for older patients with presbyopia. When this point is improved, this device will be more acceptable for older patients and its therapeutic usefulness will be further enhanced.

In summary, this study pointed out the clinical usefulness of FP Diskus®, as its handling was not signifi-
cantly affected by the aging factor, along with a recommendation to its therapeutic use as a sophisticated device for older asthmatic patients.

REFERENCES


