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Inhaled flow and Handling of Fluticasone Diskhaler by Asthmatic Patients

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We investigated the inhaled flow and handling of a Fluticasone Diskhaler (FDH) by patients familiar with the beclomethasone dipropionate inhaler (BDI), a metered dose inhaler. Before the FDH was introduced in our hospital, 174 patients were instructed in the use of the Diskhaler and measured the flow of Diskhaler inhalation. Three months after the introduction of the FDH, approximately 95 patients were using them. During their regular visit to the hospital, we checked the patients' handling of FDH and the flow of FDH inhalation (n=81). It was found that only 22% of the patients correctly handled the FDH. The major erros concerned breath-holding and disk rotation after use, but 9.9% of the patients handled the inhaler with serious error, e. g., incomplete puncturing of the blister. The mean FDH flow was 86.5 L/min, which was significantly higher than that recorded at the first FDH trial (69.1 L/min). In 9.9% of the patients, the inhaled flow was inappropriately low (<50 L/min), in 29.6% of the patients, it was unnecessarily high (>100 L/min). In conclusion, handling the FDH is easy for patients who are already familiar with the BDI. However, in 40% of the patients, the inhaled flow rate was not sufficient.

Key words : Dry powder, Inhaled steroid, Bronchial asthma, Flow of inhalation

INTRODUCTION

The Fluticasone Diskhaler (FDH), a breath-actuated dry powder steroid inhaler, was introduced in Japan at the end of 1998. Although the Diskhaler was originally designed to permit inhalation of drugs without the use of propellant gas, it was found to be advantageous in that the device requires neither a spacer nor breath synchronization. The FDH is now expected to contribute to asthma therapy because of its easy handling, and also because of the efficacy and safety of the fluticasone propionate inhalant [1]. Several studies have reported good acceptance of the Diskhaler by asthmatic patients [2-4], most of used the Diskhaler correctly even during their first exposure to the device. However, in these studies, the Diskhaler was used with a beta stimulant or some other bias such as repeated checks of handling. We considered whether similar good handling can be found with the steroid containing Diskhaler. Another problem appearing in the studies was that the flow of Diskhaler inhalation was not estimated. Although many patients with chronic asthma are familiar with a metered dose inhaler containing beclomethasone dipropionate (BDI), it remains unclear whether or not FDH, which requires a faster inhaling flow [4, 5], was appropriately inhaled.

SUBJECTS AND METHOD

In December 1998, before the FDH was introduced at the Tokai University Hospital, we held a lecture for patients about FDH. One hundred and seventy five patients voluntarily attended the lecture. The mean age was 53.2 (range 15-80) years, and the male vs. female ratio was 0.42: 0.58. Each patient was given a Diskhaler and a Rotadisk containing lactose powder (see Fig. 1). They then received a one hour lecture about the FDH, why and how to use the device, and finally were shown a six-minute video con-

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cerning the best method of using the device (Nippon Glaxo, 1998). The video encouraged the patients to inhale the FDH with a fast and deep breath. Then the patients were asked to answer questionnaires about FDH handling (Table 1), and to measure the flow of FDH inhalation. The questionnaires were designed with reference to previous reports [2, 3, 4]. In January 1999, all patients with chronic asthma using BDI were asked to change from BDI to FHD because of worldwide prohibition of Freon gases. If the

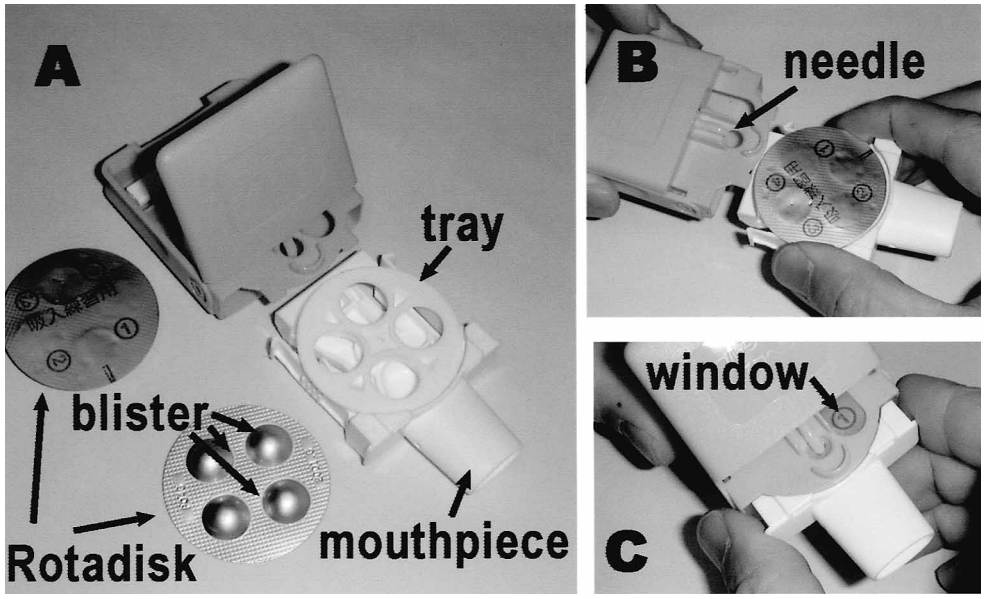

Fig. 1 A: Structure of a Fluticasone Diskhaler. Each Rotadisk contains four blisters in which the dry powder of Fluticasone propionate is stored. B: How to set the Rotadisk in the Diskhaler. C: Puncturing a blister.

Table 1 Number of patients with inappropriate Diskhaler handling

	At first experience (n=174)	After 3 months' experience (n=81)
1-1. Removed mouthpiece cover	0	0
1-2. Withdrew tray	1	0
1-3. Removed tray	3	1
1-4. Loaded Rotadisk into Diskhaler	0	0
1-5. Restored tray	3	0
1-6. Rotated Rotadisk to window #4	0	16
1-7. Checked window #	2	8
2-1. Punctured blister top and bottom	1	6
2-2. Held Diskhaler horizontally	2	15
2-3. Exhaled to residual volume	2	2
2-4. Exhaled away from mouthpiece	2	1
2-5. Side holes of mouthpiece not obstructed	1	1
2-6. Inhaled properly	3	5
2-7. Hold breath for five seconds	0	41
2-8. Rotated Rotadisk to next full blister	3	11

patient wished to change, then BDI was replaced by the FDH. At this occasion, precise instructions for FDH usage were again given to individual patients. Since then, however, follow-up instructions for FDH usage have not been given to the patients. In April 1999, when the patients using the FDH visited the outpatient clinic for a regular visit, they were asked to inhale in their usual manner in front of a registered nurse, who then checked the patient's handling of FDH according to the questionnaires. Additional questions about the patients' satisfaction with the FDH (Table 2) were also asked. Patients were once again asked to measure the flow of FDH inhalation.

The device used to measure the flow ($\dot{V}$) of FDH inhalation has been described elsewhere [6]. In brief, the device measures the peak negative pressure (Paw) in the mouthpiece of the Diskhaler. As shown in Fig. 2, the Paw is extremely and significantly linearly correlated with the power of inspiratory flow ($\dot{V}$), as measured either by pneumotachometer or hot-wire flowmeter. We examined 29 Diskhalers from different lots. The mean ± SD of correlation coefficient of the Paw-$\dot{V}^2$ relationship was 0.98 ± 0.01. When an equation, $\dot{V} = A \times \mathrm{sqr}(-\mathrm{Paw} + C)$ was assumed, the means of the parameters were $A = 16.63 \pm 1.62$ and $C = -2.57 \pm 1.44$. In the present study, we measured the Paw by connecting a plastic tube to a commercially sold digital barometer (accuracy, ± 0.3%; Akizuki-Denshi, Akihabara, Tokyo) installed in a small box (12 × 8 × 3 cm). The $\dot{V}$ was calculated from the Paw.

RESULTS

Among the patients that attended the FDH lecture, 174 individuals answered the questionnaires. Only 6.6% of the patients reported that he or she had any problems with the FDH. The most frequent problems included difficulties in properly inhaling (1.9%) and the rotation of the Rotadisk (1.9%) (Table 1).

Figure 3 shows the mean flows of the FDH inhalation in the 165 patients who agreed to the flow measurement at the FDH lecture. The mean flow was 69.1 ± 25.6 L/min (mean ± SD). It should be noted that 38.3% of the patients inhaled with a flow of less than 60 L/min and 25.4% with a flow less than 50 L/min. Patients who inhaled with a flow of higher than 100 L/min comprised 11.5% of the total number of study participants.

Despite our advice, many patients did not wish to use the FDH. The major reason given was that they were unable to visit the hospital regularly on a weekly or biweekly basis. In the Japanese medical system, new drugs cannot be prescribed for long intervals. Of those patients who did start using the FDH, eight failed to continue either because their asthma symptoms did not improve (n = 4) or because they experienced difficulty in frequently visiting the hospital (n = 4). In April 1999, approximately 95 patients were using the FDH. We collected data from 81 of these patients at their regular visit to our outpatient clinic. Because of time restrictions, we were unable to include the remaining patients. All patients who were asked to check their FDH usage agreed to be involved in the study. Of the 81 patients, only 52 had attended the FDH lecture.

Table 1 also shows data concerning the patients' handling of the FDH after 3 months' experience. Approximately 78% of the patients did not handle the FDH correctly. Most errors concerned breath holding (50.6%) or disk rotation after use (13.6%). As a serious error, 7.4% patients did not completely puncture the blister. Items 2−1 (complete puncture of blister), 2−4 (exhalation away from mouthpiece), and 2−5 (side holes kept open) were regarded as serious errors;

Table 2 Number of patients satisfied with the Fluticasone Diskhaler

	Yes	Undecided	No
1. FDH is easier to handle	66 (82.5%)	10 (12.5%)	4 (5.0%)
2. Satisfied with the FDH	53 (66.2%)	2 (2.5%)	25 (31.3%))
3. FDH inhalation is easier or more comfortable than BDP usage.	38 (47.5%)	27 (33.7%)	15 (18.8%)

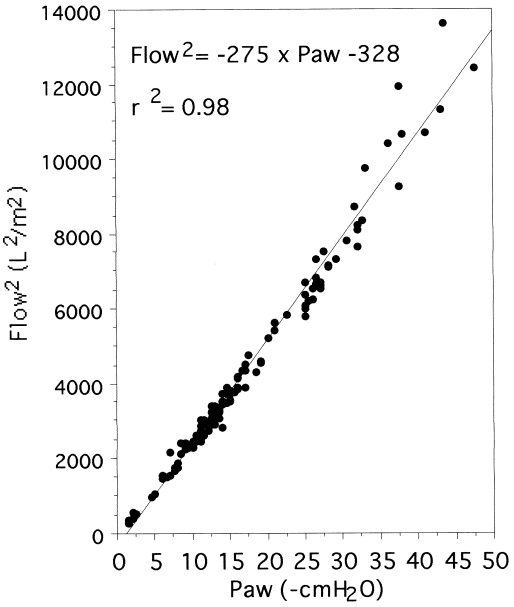

Fig. 2 The relationship between the power of inhaled flow ($\dot{V}$) and negative deflection of mouthpiece pressure (Paw) during fluticasone inhalation.

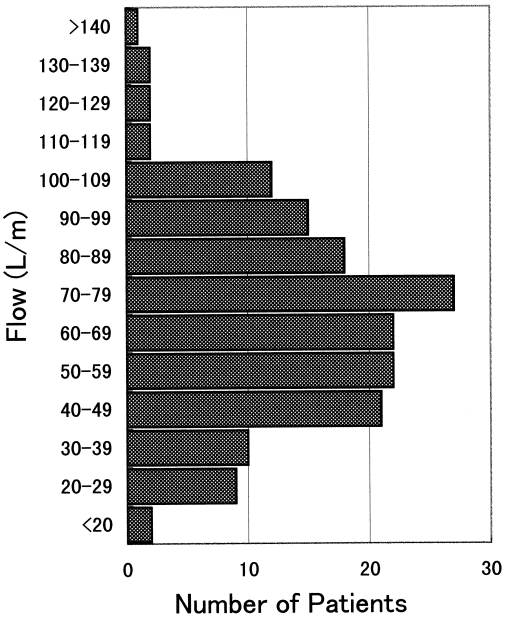

Fig. 3 Distribution of flow of fluticasone inhalation in 165 patients at the first FDH trial.

according to this rating system, 9.9% of the patients demonstrated serious problems (Table 1).

Table 2 shows satisfaction with the FDH after 3 months' experience. Approximately 82% of the patients who used the FDH felt that it was easy to handle. Those who were satisfied with the FDH comprised 66.3% of the total number of subjects. However, only 47.5% felt that FDH inhalation was easier or more comfortable than BDI. Furthermore, 33.7% remained neutral. Thirteen patients expressed dislike of the presence of residual lactose powder in the oropharynx, and five patients complained of hoarseness. A few patients did not prefer the FDH but were still using it because they agreed with the international movement to prohibit the use of Freon gases.

Figure 4 shows the flow of FDH inhalation in the 81 patients who had used the FDH for 3 months. The mean flow was 86.5 ± 26.0 L/min. In these patients, 14.8% inhaled with a flow less than 60 L/min and 9.9% with < 50 L/min. The percentage of patients who inhaled with a flow of >100 L/min was 29.6%.

In 52 patients, the inhaled flow was measured both at the first FDH trial (i.e., at the FDH lecture) and after 3 months' experience with the FDH. As shown in Fig. 5, the mean flow was significantly higher after 3 months of FDH use ($P<0.0001$ by paired *t*-test).

DISCUSSION

In the present study we found that 78% of the patients regularly using the FDH were handling it incorrectly. Most of these errors were minor problems, but serious errors were found in 9.9% of the patients. Another finding of this study was that a considerable number of the patients used the FDH with an inappropriate flow.

Regular use of inhaled steroids is now widely accepted as the primary treatment of chronic asthma [7]. However, it has also been reported [8] that numerous patients do not use inhaled steroids properly. Poor adherence to the BDI treatment is partly due to the fact that it is time-consuming and inconvenient to use [9]. In contrast, the advantage of the FDH is that the device needs neither a spacer nor breath synchronization. These differences have been highlighted in a review paper by Vaswani and Creticos [10]. Several studies have reported

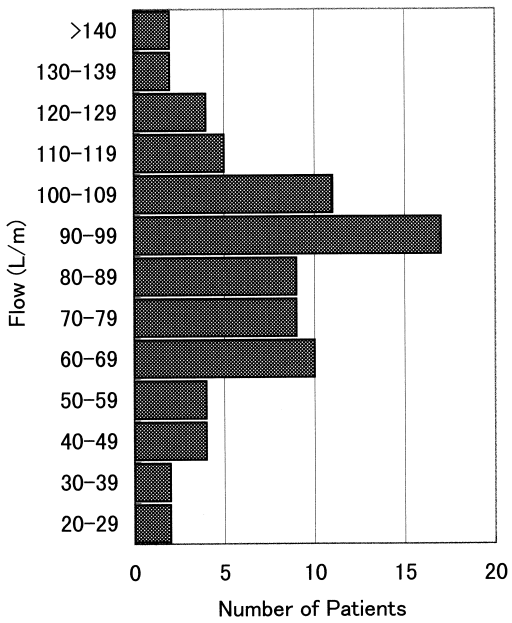

Fig. 4 Distribution of flow of fluticasone inhalation in 81 patients who regularly used the FDH.

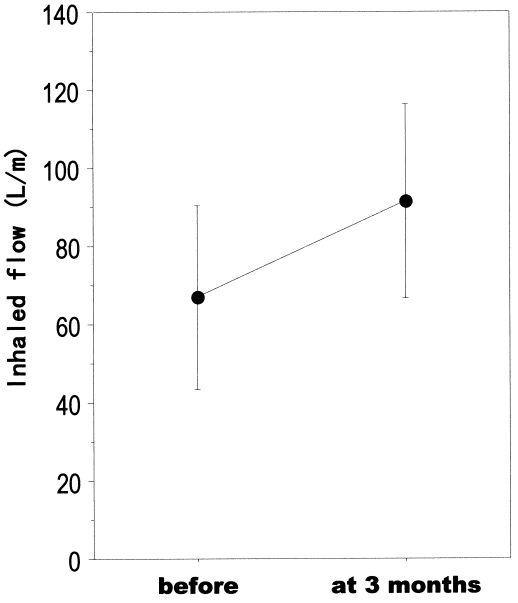

Fig. 5 Changes in mean and SD flow of fluticasone inhalation in patients, as measured before and three months after introduction of the FDH. The mean flow changed significantly ($P<0.0001$).

good acceptance of the Diskhaler [2–4]. In these reports, more than 95% of the patients achieved correct FDH performance by at most three repetitions of the instructions. Kesten et al. [2] followed up the handling of the Diskhaler 2 weeks after its introduction and found that over 95% of the patients studied maintained the correct mode of handling. In our study, more than 90% of the patients handled the FDH without having serious problems. These results are in good agreement with previous reports. In two [2, 3] such reports, the Diskhaler carried a beta-stimulant. Barnes and O'Connor [11] reported that an inhaled steroid combined with a beta-stimulant had a higher rate of adherence than did the inhaled steroid alone. This report suggests that patients would experience a better response with the proper handling of a beta-stimulant inhaler. Thus, the use of a beta-stimulant is an incentive and may have acted as a positive bias of the results. In another report [3], subjects were asked to return to the hospital every two weeks in order to be checked for the correctness of their Diskhaler handling. With repetition, subjects should show better handling techniques. In the present study, we checked inhalation with use of the steroid-carrying Diskhaler after the patients had become familiar with the device (i.e., 3 months after introduction). We asked the patients to demopsntrate their usual manner of inhaling at their regular visit. These differences may have led to the poorer results of our study in comparison to the earlier studies. However, our results may represent the ordinary or real handling of the FDH.

Another important point in this study was the quantitative analysis of the inhaled flow of the FDH. Many patients with chronic asthma are familiar with the BDI. Because these patients have been instructed to inhale beclomethasone with a low flow, they might also tend to inhale fluticasone with a similarly low flow. On the other hand, fast-flow inhalation is encouraged with the FDH (video instructions, Nippon Glaxo 1998). We considered the patients' flow rate with regular FDH use. Even after instructions for fast-flow inhalation were given, the mean flow at first visit (i.e., at the FDH lecture) was approximately 69 L/min. Although the optimal flow rate for fluticasone inhalation has

not been determined, in vitro studies with a comparable device (i.e., Diskus) demonstrated good dosing consistency, with flows as low as 30 L/min [12]. However, in our previous study [6], when the flow rate was less than 50 L/min, lactose-carriers frequently remained in the blister or tray. Thus, patients must be instructed to perform repeated inhalations when there is the presence of low inhaled flow. In patients with a flow rate of less than 60 L/min, the flow is regarded as inappropriate [12], and approximately 38% of the patients revealed this overly low flow. When the lower limit was defined as 50 L/min, 25% of the patients still were inhaling improperly. The upper limit of the flow for FDH inhalation has not yet been determined. An in vitro study with Diskus [13] showed that either a flow with 60 or 90 L/min resulted in comparable pulmonary deposition of aerosols. An in vivo study with a Diskus [14] also showed that salmeterol inhalation at 60 or 90 L/min produced almost the same improvement of $FEV_{1.0}$%. Presumably, the high flow rate of up to 90 L/min with the Diskhaler shows little difference as regards the clinical efficacy of fluticasone. Since high-inhalation flows theoretically result in reduced pulmonary deposition of aerosols [11], an unnecessarily high flow rate should be avoided. If flow rates higher than 100 L/min are regarded as inappropriate, 11.5 % of the patients should be regarded as using the FDH erroneously.

We further found that the mean flow became higher after regular use of the FDH. At three months of FDH use, the percentage of patients with a flow rate of less than 60 L/min was 14.8% and that of patients with a flow of < 50 L/min was 9.9%. On the other hand, patients with a flow rate greater than 100 L/min was 29.6%. These findings suggest that if the inhaled flow is not extremely low at the first experience of Diskhaler, instructions to inhale with a higher flow are unnecessary. Presumably a flow check after three months of FDH use is more important than it is at the first visit. However, as reported by Barnes and O'Connor [11], the slow response to inhaled steroid therapy may discourage the patients' motivation to use inhaled steroids daily. To avoid dropouts from FDH therapy, an early check of the flow using FDH inhalation may also be important.

Finally, the questionnaire about preferences and satisfaction with FDH revealed additional important information. More than 80% of the patients stated that the FDH is an easily handed device, and 66% expressed satisfaction. However, those who felt that the FDH inhalation was easierto use or more comfortable than BDI, comprised only 47.5% of the total number of patients studied. The major reason for dissatisfaction was residual powder in the oropharynx. Owing to the carrier system, Diskhaler produces fine particles with low inhaled flow rates [15]. Therefore, the lactose carrier system is essential in Diskhaler. Our findings suggest that although many patients are well-treated with the FDH, some may be candidates for non-carrier dry powder devices such as the Turbuhaler.

In conclusion, this study showed that the FDH device is easy to handle for patients familiar with BDI. However, the study also demonstrated that in 40% of the patients, the inhaled flow rate was not appropriate. Measurement of inhaled flow from the FDH may help to establish appropriate use of the device.

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