Inhalation Flow Patterns from a Dry Powder Inhaler in Patients with Bronchial Asthma: Usefulness of a Newly-designed Handy Inhalation Profile Analyzer

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Effective use of a dry powder inhaler (DPI) requires an optimal inhalation flow pattern. However, practical devices for providing instructions on flow pattern are currently unavailable. We recorded inhalation flow patterns through DPI's in 9 asthmatics (6 concurrently using Diskus, and 3 using a pMDI, -pressurized metered dose inhaler) using a new flow pattern visualizer (Visual Trainer) that displays time related changes in inspiratory flow.

Data acquisition and recording from a single DPI took 10 s, permitting ordinary clinical practice. Flows were classified into the following three patterns: an initial steep rise reaching a peak inhalation flow (PIFR) at < 0.6 s, followed by a gradual decrease with total inhalation time > 1.0 s / an initial steep rise with inhalation time < 1.0 s / an initial slow rise reaching PIFR at > 0.6 s with total inhalation time > 1.0 s. Inhalation patterns for Diskus and Turbuhaler use were evenly distributed among the three classifications. The PIFRs from Diskus tended to be higher than those from Turbuhaler in the same subjects. PIFRs using Diskus exceeded 60 L/min in all subjects, while 3 of 9 failed to reach this level using Turbuhaler. When inhaling from either DPI, PIFR appeared at > 0.6 s in 4 of 9 subjects. Inhaled volumes from Diskus were < 1 L in 3 of 9 subjects, and in 5 with Turbuhaler use. Both Diskus and pMDI users were included in the insufficient group.

In conclusion, patients using DPIs regularly do not always inhale with adequate flow patterns. The Visual Trainer may be a useful adjunct in the outpatient setting.

Key words — instructions, bronchial asthma, drug delivery, inhalation, dry powder

Introduction

With a dry powder inhaler (DPI), drug dispersion and generation of fine particles are dependent on the patients' inhalation flow. Therefore, the pattern of inhalation flow is a critical determinant of the efficiency of the DPI. For this reason the ISAM/ERS (International Society of Aerosols in Medicine/ European Respiratory Society) task force encourages inhalation with individual DPI-specific flow patterns.¹⁾ To this end devices visual-

izing inhalation flow patterns from a DPI are desirable. In a previous study,²⁾ we designed an inhalation flow visualizer and analyzed subject inhalation flow patterns from a DPI. However, for the purpose of clinical use, a much smaller, lighter, practical, and cheaper device is required which also includes a memory record for later analysis. In the present study we describe a new device, termed a "Visual Trainer", which fulfills these requirements by introducing a microcomputer into the system. The purpose of this study is to con-

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firm the practicality of the Visual Trainer in an outpatient setting and to investigate inhalation flow patterns from a DPI in asthmatic patients currently treated with a DPI using the Visual Analyzer.

Materials and Methods

This study was permitted by the Human Ethics Committee of Shonan Fujisawa Tokushukai Hospital (#14-020). **Figure 1** shows the appearance of the Visual Trainer. It is $12.5 \times 8.0 \times 3.5$ cm in size and 300 g (including batteries) in weight. The cost of its parts is 8,000 Japanese yen (approximately \$100). This system continuously measures pressure in the mouth piece of a DPI through a fine plastic tube (OD 2.0 mm, 35 cm in length). Inhalation flow rate is calculated with the equation $\text{flow} = \text{constant} \times \text{pressure}^{0.5 \ 3)}$, and is continuously displayed on a GLCD (graphic liquid cell display). The peak inhalation flow rate (PIFR), time reaching the PIFR (T_{PF}), and inhalation volume (V_I) are calculated and also displayed on the GLCD. The data of pressure changes can be stored on an SD-card for later analysis.

Figure 1 Appearance of the Visual Trainer

Changes in inhalation flow rate are displayed on a GLCD (graphic liquid crystal display) for 5.7 s. The peak inhalation flow rate (PIFR), time reaching the PIFR (T_{PF}), and inhalation volume (V_I) are also displayed on the GLCD. The data can be stored on an SD-card.

Figure 2 A block diagram of the system

Figure 2 shows a block diagram of the system. A small side hole was made at the mouth piece of the DPI, and inhalation pressure (P_{aw}) was continuously measured with a piezo-crystal transducer. The P_{aw} signals were amplified, converted with a 10 bits A to D converter, and then processed by a microcomputer (PIC4550, Microchip Technology inc. Chandler, USA). Sampling rates were each 10 ms for 0 - 1.27 s, 20 ms for 1.27 - 2.56 s, and 50 ms for 2.56 - 5.76 s. The system was triggered when P_{aw} reached a threshold. The P_{aw} signals were further converted to flow rates with the equation $\text{flow} = \text{const} \times \sqrt{\text{pressure}}^{3, 4)}$ in the microcomputer. The constant was individual DPI specific, and has been reported elsewhere.⁴⁾ The time course of variations in inhalation flow for 5.4 s was continuously displayed on GLCD. The PIFR, T_{PF} and V_I were also displayed on the GLCD (**Fig 1**). The pressure data was stored on an SD card with text format within 3 seconds.

The subjects were 9 asthmatic patients regularly visiting the outpatient clinic at Shonan Fujisawa Tokushukai Hospital. Inclusion criteria for the patients were those regularly treated with inhaled medications and asymptomatic for at least 3 months prior to the study. After explanation of the purpose and method of the study, patients participated voluntarily. Patients were asked to inhale from both Diskus and Turbuhaler each time with

the same maneuver and strength as they usually do at home. Active drugs were not contained in the DPI and which DPI, Diskus (GlaxoSmith-Klein KK, Tokyo, Japan) or Turbuhaler (Astellas Pharma, Tokyo, Japan), to inhale from first was not specified.

Results

The time to perform and record each DPI trial was approximately 10 s. Owing to this short period of examination time, ordinary clinical practice was almost unaffected by the flow-profile recordings.

Among the 9 patients, six were Diskus-users and the remaining 3 used a pMDI. Four were male and five were female. Their median age was 56 years (range 44 - 81). All the patients had been instructed in DPI use with In-Check® (Clement Clarke International Ltd, Edinburgh, UK) along with the first prescription of the DPI drug.

Inhalation flow patterns in these patients were similar to those in the previous study on healthy volunteers.^{2,5)} Thus, referring to the previous studies, we classified them into three patterns as shown in **Fig 3**. Pattern A is the ideal pattern, in which inhalation flow rises steeply in the early phase, reaching its peak within 0.6 s, and gradually decreases. In addition, total inhalation time is longer than 1.0 s. In pattern B, inhalation flow rises steeply and total inhalation time is less than 1.0 s (not a deep inhalation pattern). In pattern C, inhalation flow rises slowly, reaching the PIFR later than 0.6 s and then gradually decreases. Total inhalation time is longer than 1.0 s (late peak pattern). Of interest is that inhalation patterns were distributed evenly among the three classifications whether using Diskus or Turbuhaler (**Table in Fig 3**).

Figure 4 shows PIFR, T_{PF} and V_i during inhalation from either Diskus or Turbuhaler. The PIFR

Figure 3 Typical patterns of inhalation flow from a DPI (dry powder inhaler)

A (ideal pattern): Inhalation flow rises steeply in the early phase, reaching its peak within 0.6 s, and gradually decreases with total inhalation time < 1.0 s. B: Inhalation flow rises steeply with total inhalation time < 1.0 s. C: Inhalation flow rises slowly reaching the PIFR (peak inhalation flow rate) later than 0.6 s and then gradual decreases with total inhalation time > 1.0 s. Inset table, distribution of patient number with each inhalation pattern using either Diskus or Turbuhaler.

Figure 4 The peak inhalation flow rate (PIFR) (A), time reaching the PIFR (B), and inhalation volume (C) during inhalation from either Diskus or Turbuhaler

Filled circles: concurrent Diskus users, open circles: pMDI users.

during inhalation from Diskus tended to be higher than that using Turbuhaler in the same subject. When inhaling from Diskus PIFRs in all the subjects exceeded 60/L, while 3 out of 9 subjects did not reach this level using Turbuhaler (panel A). In either group, four of nine subjects required longer than 0.6 s to reach peak inhalation flow (panel B). In using Diskus, inhaled volumes were less than 1 L in 3 of 9 subjects, and in 5 of 9 subjects using Turbuhaler (panel C). These subjects of both groups, concurrent Diskus users (filled circles) and pMDI users (open circles) were included in the insufficient group.

Discussion

DPIs are widely used in the treatment of COPD and bronchial asthma. The use of DPIs has now extended to the inhalation of insulin. Drug dispersion and separation into fine particles from a DPI are dependent upon energy from a patient's inhalation flow, and thus inhaled flow pattern has a profound effect on DPI efficiency. An optimal inhalation flow can also impact the cost of treatment since older, cheaper drugs may be more effective than costlier newer ones if the efficiency of DPI inhalation is better with the former. How-

ever, instruction in inhalation flow with use of a DPI is not routinely given to patients. Surprisingly, devices for flow pattern instruction are universally unavailable. A few systems visualizing the time course of inhalation flow rate from a DPI have been reported.⁶⁻⁸⁾ Unfortunately, all of these systems are either complicated or expensive, and thus are not suited to use in clinical practice. Several years ago, we reported a simplified system which displays the peak inhalation pressure by measuring mouth piece pressure of a DPIs,⁹⁾ and we found that feedback of the inhalation flow rate to the patient was useful in asthma control (unpublished observation). Recently we reported another system visualizing flow transitions over time on a built-in small oscilloscope,²⁾ but this system was still too large for clinical use. The Visual Trainer was designed to achieve cost and size reductions by using a microcomputer.

The Visual Trainer is sufficiently small and light to be carried in a lab coat pocket. This is important for security and convenience. Easy handling and short operation time are also required in clinical use. Visual Trainer starts automatically and takes 6.4 s for data acquisition and 3 s for data storage on an SD card. Operation is conducted with only three switches (main, reset, go). In the present study, we completed measurements and recordings of inhalation flow patterns in 9 asthmatic patients without disturbing clinical practice. Thus, we confirmed that Visual Trainer was a convenient system to be used in an outpatient setting.

In many clinics and pharmacies, verbal instruction such as "Inhale forcefully and deeply" has sufficed for flow instructions. As has been reported,²⁾ this constitutes inadequate and ineffective instruction, especially for those who are not familiar with a DPI. In-Check® and other inhalation trainers

are sometimes used to supplement inhaling flow instruction. These devices indicate either the peak inhalation flow or when some threshold flow during inhalation had been exceeded. However, as reported by Bissgard *et al.*,¹⁰⁾ in most cases, when inhalation flow reached its peak, drugs dispersion had already taken place. Thus, whether the highest flow appears in the very early phase of inhalation should be identified with DPI instruction.

In the present study we found that even in those who regularly use DPIs, the inhalation patterns were not necessarily satisfactory. The ideal inhalation pattern through a DPI was proposed in the ISAM/ERS report,¹⁾ but quantitative parameters were not included. A PIFR of 60 - 100 L/min is agreed upon in most of the literature. However, a suitable flow acceleration, *ie* the time to reach PIFR, is not clear. Bissgard *et al.*¹⁰⁾ reported that the peak inhalation time through Turbuhaler was 0.36 ± 0.23 s (Mean $\pm$ SD) and that through Diskus was 0.46 ± 0.31 s in well trained subjects, while the peak of drug dispersion was 0.19 ± 0.03 s and that for Diskus was 0.16 ± 0.14 s. Therefore, coinciding peak inhalation flow with peak of drug dispersion is difficult. We decided the ideal peak time to be less than 0.6 s since, in our previous study on the inhalation trainer⁵⁾ in healthy adults, the time to peak inhalation flow through Diskus was 0.44 ± 0.17 s and that through Turbuhaler was 0.53 ± 0.23 s. Deep inhalation has theoretical advantages for drug delivery¹¹⁾ and an inspiratory volume of 80% vital capacity is recommended in pMDI use.¹²⁾ Once drug has been dispersed from a DPI, inhalation flow rate should be low to avoid precipitation in the upper airway. Studies on pMDI's suggest that a suitable flow after drug dispersion is approximately 30 L/min.¹¹⁾ It should be noted that the value of PIFR has less influence on drug dispersion from Diskus than that from

Turbuhaler,¹³⁾ and high acceleration flow is not required in a capsule type DPI.¹⁾

As shown in **Fig 3**, even among those who were well controlled with DPI's, an ideal inhalation pattern was seen in only 2 of 6 subjects using Diskus. Another finding was that the distribution of inhaled flow patterns of DPI users was not different from those unfamiliar with a DPI, such as pMDI users. While inhalation patterns were not dependent on each DPI the peak inhalation flows from Turbuhaler tended to be lower than those from Diskus (**Fig 4**). Therefore, a stronger inhalation should be advised when the DPI is changed from Diskus to Turbuhaler, and with the order reversed, a weaker inhalation may reduce pharyngeal effects. There are large variations in measured parameters from individual subjects in the panels A - C. We obtained similar wide variations in our previous study on healthy subjects who were familiar with DPI's.¹⁴⁾ Therefore, such wide variations may not arise from inexperience with a new DPI, *ie*, the device that the subject had not previously used. Statistical analysis was not done since we examined only a small number of subjects in this preliminary study. However, these findings suggest the importance of flow pattern instruction in the use of DPIs.

In conclusion, the present study suggests that patients, even those who use a DPI regularly, do not always inhale with a satisfactory flow pattern. Visual Trainer has the potential to improve flow pattern in those patients. Visual Trainer may be a convenient system to use in an outpatient setting.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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