Relationship between Amount of Drug Delivered to Lungs and AmountReleased from Diskhaler by Inhalation with Tapping

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Received December 20, 2006; accepted April 3, 2007; published online April 6, 2007

It is well known that drug residue remains in a fluticasone propionate Diskhaler (FP-DH) following a single inhalation. Thus, the inspiratory ability of the patient has an influence on the effects of the drug. In a previous study, we reported that the amount of drug remaining in an FP-DH was decreased by tapping the device after the first inhalation. In the present study, we investigated the relationship between the amount of drug delivered to the lungs and amount of drug released from the FP-DH by inhalation along with tapping using an in vitro model. We measured the amounts delivered to the throat, stage 1, and stage 2 of a twin impinger device by HPLC-UV, following inhalation and tapping of 100 µg of FP-DH at various inspiratory flow rates, which ranged from 11.5 to 73.6 l/min for 2 s. A positive linear correlation between the amount of drug released from the FP-DH and that deposited in stage 2 was observed. Amounts deposited in stage 2 following tapping were estimated to be 6.0 µg at an inspiratory flow rate of 20 l/min and 10.6 µg at 60 l/min, while those without tapping were 2.0 µg and 10.2 µg, respectively. Notably, at an inspiratory flow rate of 20 l/min, the amount of drug deposited in stage 2 by tapping was increased about 3-fold in comparison to that without tapping. Our results indicate that the amount of drug deposited in stage 2, i.e., the lung in our model, is increased by tapping of the device, which would be particularly helpful for patients with a lower level of inspiratory ability.

Key words Diskhaler; lungs; device tapping; inspiratory flow rate; fluticasone propionate

Fluticasone propionate is a commercially available dry powder inhaler that utilizes a Diskhaler. The Diskhaler is a device that accommodates reloadable disks that contain four numbered aluminium foil blisters filled with drugs, formulated with a lactose carrier. Prior to use, the disk is loaded into a cartridge unit and slid into the outer body, which has a hinged lid, a piercing needle, and a dosage-viewer. During use, the device must be kept level while piercing the blister, and the patient is instructed to inhale ‘quickly and deeply’ through the mouthpiece. Some amount of drug residue is known to remain in the fluticasone propionate Diskhaler (FP-DH) following a single inhalation, therefore, the patient information pamphlet notes; “Please inhale more than once or twice, as some amount of drug will remain in the device after a single inhalation.” Further, it has been proposed that the inspiratory ability of the patient has an influence on the amount remaining in the device.1,2) Since dosing performance of an FP-DH is likely dependent on patient inspiration capability, the method of inhalation is important clinically for delivery of the proper dosage. In our previous study, patients found some amounts of drugs remaining in the device after a single inhalation with an FP-DH, while those remaining after a second inhalation were decreased by tapping the device after the first inhalation.3) We also found a relationship between peak inspiratory flow rate and amount of drug released from the device, but did not clarify the change in amount of drug delivered into the lungs by tapping. In the present in vitro study, we investigated the relationship between the amount of drug delivered into the lungs and the amount released from the device when tapping was utilized, by quantification of the amount of FP following inhalation with an FP-DH equipped with a twin impinger at various inspiratory flow rates.

MATERIALS AND METHODS

Materials A Flutide® 100 Rotadisk® (GlaxoSmithKline K.K., Lot No. 355) was used as the FP-DH device in the present study. To investigate the amount of drug inhaled, we used an inhalation simulator (Fig. 1), which consisted of a flow recorder placed in a plastic air-tight box that covered the FP-DH equipped with a twin impinger and a vacuum pump. The FP-DH was kept at an angle of 90° to the inlet of the twin impinger and the inspiratory flow rate was recorded using a Vitalograph® 2120 Handheld Storage spirometer (Vitalograph Ltd.). The data was transferred to a computer and analyzed using Vitalograph Spirotac® IV software (Vitalograph Ltd.). The relative amounts of drugs distributed in the throat (A), stage 1 (upper impinger) (B), and stage 2 (lower impinger) (C) of the twin impinger (Fig. 1) were determined by measuring the amounts in each of those areas. The experiments were performed at 20 °C with a relative humidity of 30%. The inhalation time was set at 2 s, based on the results of a preliminary experiment of inhalation performed by a human subject as quickly and deeply as possible. In a report

Fig. 1. System for Measurement of Peak Inspiratory Flow Rate and Delivered Doses to Each Part of the Twin Impinger Device

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of 31 stable asthma patients who inhaled FP-DH through a Diskhaler device set for optimal resistance and had their peak inspiratory flow rate measured using an In-Check Meter, the peak inspiratory flow rates ranged from 40 to 130 l/min. In another study of 93 asthma patients who inhaled with an FP-DH for the first time, the range of peak inspiratory flow rates was from 18.0 to 141.3 l/min. Therefore, peak inspiratory flow rates were set from 11.5 to 73.6 l/min in this study, since such peak inspiratory flow rates vary widely and some amounts of drug remained in the FP-DH following inhalation by patients with a low level of inspiratory ability less than 60 l/min in particular. The technique used for tapping the device was three taps on the upper area of the rear side of the device by use of a fingernail, while being careful not to disperse the drugs outside of the device. During the experiments, the plastic box was opened after the first inhalation of drugs contained in a single blister and the second inhalation was carried out after tapping. All experimental procedures were carried out by the same person. The inspiratory flow rate of the second inhalation was the same as that of first inhalation.

**Measurement of Drug Amounts**

Drugs that adhered to each component of the system (A, B, C) were washed using 50 ml of a 10:7:3 mixture of methanol, water, and acetonitrile after the second inhalation. These samples were then assayed using high performance liquid chromatography with ultraviolet detection.

**Relationship between Amount of Drug Released from FP-DH and Amount Deposited in Stage 2**

The relationship between peak inspiratory flow rate and amount of drug released from the FP-DH was analyzed using Eq. 1, where \( R_0 \) was the initial rate of drug released, \( K_R \) the constant of the rate to release a 50% dose of dry powder, and \( D_{\text{max}} \) was the maximum dose released from the device. The constants \( R_0 \), \( K_R \), and \( D_{\text{max}} \) were estimated by substitution of the measured values of the doses released from the device at various peak inspiratory flow rates (R) in Eq. 1. The dose \( D_R \) released from the device was considered to be the total sum of the amounts in the throat (A), stage 1 (B), and stage 2 (C) (Fig. 1).

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D_R = \frac{D_{\text{max}} \cdot (R - R_0)}{K_R \cdot (R - R_0)}
\]  

Next, the relationship between the amount of drug released from the device and amount deposited in stage 2 was analyzed. The amount of drug deposited in stage 2 was calculated from the peak inspiratory flow rate, by integration of Eq. 1 and the relationship mentioned above.

**RESULTS**

**Measurement of Drug Amounts**

Figure 2 shows the relationship between peak inspiratory flow rate and drug amounts deposited in each component of the twin impinger (A, B, C). The doses delivered to the throat (A), stage 1 (B), and stage 2 (C) increased as the peak inspiratory flow rate increased.

**Relationship between Amount of Drug Released from FP-DH and Amount Deposited in Stage 2**

Figure 3 shows the doses released from the device and fitted curves obtained from Eq. 1 for the various peak inspiratory flow rates with tapping of the device (shown as closed circles and solid curve). Previously, we reported drug amounts after a single inhalation without tapping of the device (shown as open circles and dot curve in the figure) using a similar experimental apparatus. The fitted curves were well matched to the values obtained in the experiment. Each parameter was determined from the measured amounts of drugs released from the device at various peak inspiratory flow rates using Eq. 1. Table 1 shows the determined parameters with tapping of the device.
device as compared to a single inhalation without tapping.

The estimated values for $K_R$ and $R_0$ with tapping were lower than those without, with a significant difference observed for $R_0$ ($p<0.01$). With tapping and a low inspiratory flow rate, the amounts of drugs released from the device increased and those deposited in the lungs were estimated to be high.

Figure 4 shows the relationship between the amount of drug released from the device and amount deposited in stage 2 with (closed circles) and without (open circles) tapping after a single inhalation. The relationships were similar for each method of inhalation. Further, a positive linear correlation between the amount of drug released from the device and amount of drug deposited in stage 2 was observed, as the lines were similar ($r=0.905, p<0.001$). Equation 2 shows the relationship between the amount of drug released from the device and the amount deposited in stage 2.

$$D_{ST2} = 0.147 \cdot D_R - 0.492$$

$D_{ST2}$ represents the amount of drug in stage 2. Equation 3 is composed of Eqs. 1 and 2. Figure 5 shows the estimated dose deposited in stage 2 using Eq. 3 with various peak inspiratory flow rates. The curves generated from the estimated values were well matched to the values obtained in the experiments.

$$D_{ST2} = 0.147 \cdot D_{max} / (K_R + (R_0 - R_0)) - 0.492$$

The amounts deposited in stage 2 with tapping were 6.0 $\mu$g at an inspiratory flow rate of 20l/min, 8.2 $\mu$g at 30l/min, 9.4 $\mu$g at 40l/min, 10.6 $\mu$g at 60l/min, and 11.3 $\mu$g at 90l/min. On the other hand, those amounts without tapping were 2.0 $\mu$g, 6.2 $\mu$g, 8.2 $\mu$g, 10.2 $\mu$g, and 11.5 $\mu$g, respectively.

### DISCUSSION

We recently reported that the amounts of drugs remaining in an FP-DH were decreased by tapping the device after the first inhalation in patients with low inspiratory capabilities. In the present study, we investigated the relationship between the amount of drug released from the FP-DH and amount delivered to the lungs following inhalation using an in vitro experimental model of inhalation with and without tapping. With our experimental device, the technique for tapping of the device was three taps on the upper area of the rear side of the device by use of a fingernail, while being careful not to disperse the drugs outside of the device.

There was a significant relationship between the amount of drug released from the device and amount of drug deposited in stage 2 using the usual method of inhalation (i.e. a single inhalation without tapping) in the present study. Further, there was a positive linear correlation between the amount released from the device and amount deposited in stage 2 with and without tapping (Fig. 4). It was considered that amount of drug in the lungs would be increased as the amount released from the device was increased. Therefore, we concluded that the dosage in the lungs would be increased if inhalation was performed using the present method of tapping of the FP-DH by patients with lower levels of inspiratory ability.

Regarding the relationship between inspiratory flow rate and drug remaining in an inhalation device, Ohbayashi et al. reported a method of coordinated inhaling and tapping several times for each blister using 70 patients with asthma. Three months after treatment using that method, peak expiratory flow (PEF) values were significantly superior to those obtained at the beginning of the study. Those results indicated that the amount of drug delivered to the lungs was increased by tapping. However, the method was difficult for the patients to perform, because they were required to tap the device with one hand while holding it with the other hand during inhalation.

In the present study, we considered that amount of drug deposited in stage 2 was increased by tapping of the device at a lower inspiratory flow rate (Fig. 5). Our results suggest that the present method of inhalation with tapping was useful for
increasing the amounts of drugs delivered to the lungs, especially in patients with lower inspiratory flow rates. At an inspiratory flow rate of 60 l/min, the amount of drug deposited in stage 2 was estimated to be 10.6 μg with tapping and 10.2 μg without tapping, which were not significantly different. On the other hand, at an inspiratory flow rate of 20 l/min, the amount of drug deposited in stage 2 was estimated to be 6.0 μg with tapping, which was an approximately 3-fold increase over that without tapping.

In conclusion, the present method of inhalation with tapping of the FP-DH was easy to perform and useful for increasing the amounts of drugs delivered to the lungs, especially in patients with a low level of inspiratory ability or when a large amount remained in the device after the first inhalation.

**REFERENCES**