Analysis of Relationship between Peak Inspiratory Flow Rate and Amount of Drug Delivered to Lungs Following Inhalation of Fluticasone Propionate with a Diskhaler

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A Diskhaler is a dry powder type of inhaler that utilizes a breath controlled drug delivery system. The inspiratory flow rate of the patient would have a significant influence on the effects of drugs administered by a Diskhaler. Thus, we investigated the relationship between inspiratory flow rate and amount of drug delivered into the lungs when using a fluticasone propionate dry powder inhaler with a Diskhaler (FP-DH). To investigate the amount of drug inhaled, we used an inhalation simulator, 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. Drugs located in a plastic box, as well as the device, throat, and stage 1 and stage 2, were assayed by HPLC-UV, following in vitro inhalation at the various flow rates ranging from 18.7 to 77.3 l/min for 2 s. The relationship between peak inspiratory flow rate and amount of drug released from the device was analyzed. A positive linear correlation between the dose released from the device and amount of drug deposited in stage 2 was observed (r=0.899, p<0.001). The doses deposited in stage 2 were estimated to be 2.9 μg at a flow rate of 20 l/min, 6.6 μg at 30 l/min, 8.4 μg at 40 l/min, 10.1 μg at 60 l/min, and 11.3 μg at 90 l/min. It was suggested that the amount of drug in the lungs decreased along with a decrease in peak inspiratory flow rate when it was lower than 60 l/min. Our results were found to be very useful to estimate lung deposition by using peak inspiratory flow rate for administration planning, especially in patients with a flow rate of less than 60 l/min.

key words fluticasone propionate; dry powder inhaler; Diskhaler; inspiratory flow rate; drug delivered to lung

Materials and Methods

Materials A Flutide® 100 Rotadisk® (GlaxoSmithKline K.K., Lot No. 355) was used as the FP-DH in the present study. A blister contains a mixture of 100 μg of microfine FP blended with lactose to a total weight of 25 mg. Geometric particle size of FP was ≤5 μm (90%< of particles),7) aerodynamic particle size of FP was 3.3 μm,8) and geometric particle size of lactose was 60—90 μm.7) 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 angle of 90° to the inlet of the impinger. The flow rate was recorded using a Vitalograph® 2120 Handheld Storage spirometer (Vitalograph Ltd.), and data was transferred to a computer and analyzed using Vitalograph® Spirotrac® IV software. The relative amounts of the drug distributed inside a plastic box (a), and the device (b), throat (c), stage 1 (upper impinger) (d), and stage 2 (lower impinger) (e) were determined by measuring the amounts of drugs in those areas. The experiments were performed at 20°C with 30% relative humidity. The flow rates ranged from 18.7 to 77.3 l/min for 2 s. Measurement of FP Drugs adhered to each component

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of the system were washed using 50 ml of a 10:7:3 mixture of methanol, water, and acetonitrile. These samples were then assayed using high performance liquid chromatography with ultraviolet detection (HPLC-UV).9)

Analysis of Relationship between Peak Inspiratory Flow Rate and Amount of Drug Released from the Device

The relationship between peak inspiratory flow rate and amount of drug released from the device was analyzed using Eq. 1, where \( R_0 \) is the initial rate of drug released, \( K_R \) is the constant of the rate to release a 50% dose of dry powder, and \( D_{\text{max}} \) is the maximum dose released from the device. In previous study using a cascade impactor by a flow rate ranging from 20 to 60 l/min, the amounts of drug residues were decreased in a nonlinear manner as the peak inspiratory flow rate increased.3) From the results, it was thought that the relationship between peak inspiratory flow rate and amount of drug released from device was a threshold for force releasing powder by that flow rate range. Thus, we analyzed using an equation of saturation curve for characteristic of drug released from 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 amount of powder inside the plastic box \( (a) \), throat \( (c) \), stage 1 \( (d) \), and stage 2 \( (e) \) (Fig. 1).

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

Analysis of Relationship between Amount of Drug Released from the Device and Amount of Drug Deposited in Stage 2

The relationship between amount of drug released from the device and amount of drug deposited in stage 2 was analyzed. And, the amount of drug deposited in stage 2 was estimated by both provided relationship and Eq. 1 by using the peak inspiratory flow rate.

RESULTS

Measurement of FP

Figure 2 shows the relationship between peak inspiratory flow rate and amount deposited inside the plastic box \( (a) \), device \( (b) \), and twin impinger areas \( (c, d, e) \). The total amount recovered (sum of \( a \), \( b \), \( c \), \( d \), and \( e \)) was 97.3 ± 5.7 μg (mean ± S.D.), which was considered to be very good. The amount of powder dispersed outside of that considered to be inhaled (Fig. 1, \( (a) \)) was 1.0 ± 0.4 μg, which was independent of the peak inspiratory flow rate. The remaining dose in the FP-DH decreased in a nonlinear manner as the peak inspiratory flow rate increased, whereas the doses delivered to the throat, stage 1, and stage 2 of the twin impinger increased as the peak inspiratory flow rate increased.

Analysis of Relationship between Peak Inspiratory Flow Rate and Amount Released from the Device

Figure 3 shows the doses released from the device and the fitted curve from Eq. 1 at various peak inspiratory flow rates. The fitted curves were well matched to the values obtained in the experiment. Each parameter was estimated from the measured amounts of drugs released from the device at various peak inspiratory flow rates using Eq. 1, which yielded estimated values for \( D_{\text{max}} \), \( R_0 \), and \( K_R \) of 99.0 ± 11.0 μg, 16.8 ±

\[ D_{\text{ST2}} = 0.129 \cdot D_R + 0.748 \]

\( D_{\text{ST2}} \) is amount of drug in stage 2. Equation 3 was then integrated from the correlation mentioned above and the result of Eq. 1. Figure 5 shows the estimated doses deposited in stage 2 using Eq. 3 with various peak inspiratory flow rates.
Inhalation of corticosteroids is an important first line of defense in anti-inflammatory therapy and the drugs have become primary agents for treatment of asthma. A metered dose inhaler (MDI) was previously used for airway diseases, however, it requires coordinating actuation with the start of slow inhaling. Thus, DPIs are now used for the delivery of drugs into the lungs of asthma patients.\(^1\) In the Patient Information Leaflet given with a DPI, the instructions state that the user should “suck in through your mouth as quickly and as deeply as you can,” thus the performance of a DPI is dependent on the inspiratory effort of the patient. However, it has been reported that patients with a lower inspiratory flow rate received an insufficient clinical effect from use of the device.\(^2\) In the present study, we investigated the relationship between peak inspiratory flow rate and amount of drug delivered to each component of a Flutide\(^3\) 100 Rotadisk,\(^4\) with a twin impinger utilized as a DPI in an \textit{in vitro} apparatus.

To deposit the drug into the lungs, the Diskhaler utilizes a coarse mesh to produce turbulence in the stream of air inhaled through the mouthpiece \textit{via} a pierced blister, which de-aggregates the fine particles from the coarser lactose carrier using small air holes on either side of the mouthpiece and a fast peak inspiratory flow rate. We considered that it was possible for the drugs to be dispersed from the air holes, however, the amount dispersed was 1.0±0.4 \(\mu g\), \textit{i.e.} a minimum dose that had no association with peak inspiratory flow rate.

There have been several reports on the relationship between peak inspiratory flow rate and drug delivered by various systems,\(^3,4\) with a Diskhaler shown to deliver approximately 12\% of the initial dose.\(^11,12\) The present results support and confirm those previous studies, as the estimated amount of drug deposited in stage 2 was 10.1 \(\mu g\) at a flow rate of 60 \(\text{l/min}\), adequate for obtaining a good effect from a Diskhaler and similar to the 12\% reported previously. Moreover, the amount of drug deposited in stage 2 at a flow rate of 60 \(\text{l/min}\) was 10.1 \(\mu g\) and slightly increased to 11.3 \(\mu g\) at 90 \(\text{l/min}\). Thus, with these range of flow rates, there were no differences in the amounts of drug deposited observed. In a previous comparison between flow rates of 60 and 90 \(\text{l/min}\) with a Diskhaler, it was reported that the amount of drug deposited in stage 2 of a twin impinger device was unaffected by peak inspiratory flow rate.\(^5\) That is, if the peak inspiratory flow rate was 60 \(\text{l/min}\) or more, the influence of flow rate was scant, which was confirmed in the present study. On the other hand, the estimated values ranged from 2.9 to 10.1 \(\mu g\) at flow rates between 20 and 60 \(\text{l/min}\), which increased as the flow rate was increased. It was suggested that, should the rate be lower than 60 \(\text{l/min}\), it would have a major impact on peak inspiratory flow rate. The amount of drug in the lungs decreased along with a decrease in peak inspiratory flow rate when it was lower than 60 \(\text{l/min}\).

Our results showed that it was possible to estimate the amount of drugs deposited in stage 2 by using Eq. 3 with substitution of the peak inspiratory flow rate. We considered that correct use of the FP-DH would be possible if the amount of drug deposited in stage 2 was first estimated using our method, after which an individualized dosage plan for the patient could be drawn up based on the estimated value, especially in patients with a flow rate of less than 60 \(\text{l/min}\).

**REFERENCES**

7) Drug Information Booklet of Flutide\(^3\) Rotadisk.\(^8\)