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Note

Resistivities of placebo and active Diskus® inhalers compared

Mariëlle E.A.C. Broeders *, Johan Molema, Hans Th.M. Folgering

Department of Pulmonology Dekkerswald, University of Nijmegen, P.O. Box 9001, 6560 GB Groesbeek, The Netherlands

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Abstract

Objective: Verbal instruction and demonstration of inhalation technique are essential to enhance the effectiveness of inhalation therapy. Placebo devices are commonly used to instruct patients. It is not obvious that patients, who inhale with an adequate flow through an empty placebo Diskus®, would also be able to do so with active inhalers containing a strip with powder. The presence of powder may result in a change in resistivity. We compared the resistivities of a placebo Diskus® being empty; a powder filled Diskus® inhaler and a Diskus® inhaler with an empty blister. *Methods:* A Diskus® inhaler was placed in a box, which enabled measurement of pressure drop and flow rates. Ten placebo and ten Ventolin® Diskus® inhalers were measured. Twelve pressure- and flow-profiles were recorded through each device. After each simulated inhalation through a powder filled blister, a second inhalation was performed through the empty blister. The resistivity was calculated by pressure-flow equation. *Results:* The resistivity of the empty placebo Diskus® inhaler was slightly but significantly higher than both blister filled inhalers, with or without powder (0.0215 vs. 0.0211 and 0.0211 $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$) ($P < 0.001$). *Conclusion:* Patients who are capable of generating sufficient flow through a placebo Diskus® will surely be capable of generating equivalent flows through a Diskus® inhaler containing a strip with active drug substance.

Keywords: Inhalation therapy; Instruction; Diskus® inhaler; Resistivity

1. Introduction

The effectiveness of inhalation therapy highly depends upon an adequate inhalation technique. Many patients with asthma and COPD use their inhalation device inadequately (van der Palen et al., 1995). Studies have shown that written instructions alone are not sufficient, supplementary verbal instructions, demonstrations and practice sessions are needed (Cochrane et al., 2000). Medical personnel commonly use placebo devices to instruct patients. In case of use of a Dry Powder Inhaler (DPI), special attention should be given to the inspiratory flow generated by the patient.

* Corresponding author. Tel.: +31-24-68-59911; fax: +31-24-68-59290.

E-mail address: m.broeders@mailbox.kun.nl (M.E.A.C. Broeders).

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Drug delivery by DPIs depends on the inbuilt resistivity of the inhaler and the inspiratory flow generated by the patient (Ganderton, 1997). Patients must be able to generate a sufficient inspiratory flow in order to release the powder and deaggregate the drug to generate respirable particles. Consequently, lung deposition will generally increase at higher inhalation flows (Pauwels et al., 1997).

There is a linear relationship between the inspiratory flow-rate and pressure drops of inhalation devices (Clark and Hollingworth, 1993). So, by a given PIFR and PPD, the resistivity of the device can be calculated as the slope of this relationship. A higher device resistivity requires a higher patients' effort to generate enough flow to disperse the powder. On the other hand a higher device resistivity generates a higher turbulence, leading to a better dispersion (Srichana et al., 1998).

The placebo Diskus® inhaler contains no blisters, in contrast to the active device, which contains a strip with blisters with lactose and the active drug substance.

It is conceivable that a patient, who can generate an adequate inspiratory flow through an empty placebo inhaler, might not be able to generate an equivalent flow if the inhaler contains powder filled blisters which may induce a change in resistivity.

This study was undertaken to investigate the possible difference in resistivity between a placebo Diskus® (PlcD); a powder filled blister Diskus® (PwD) and a Diskus® inhaler with an empty blister (EBD).

2. Methods

An experimental set-up was constructed according to Fig. 1.

The Diskus® inhaler was placed in a specially constructed airtight box, which allowed measurement of pressure drops and flow rates by two Inhalation Profile Recorders (GlaxoSmithKline Research & Development, Ware, UK (Bisgaard et al., 1998)).

A pressure-probe measured the pressure ($P1$) at the mouthpiece of the Diskus®. The Pressure-

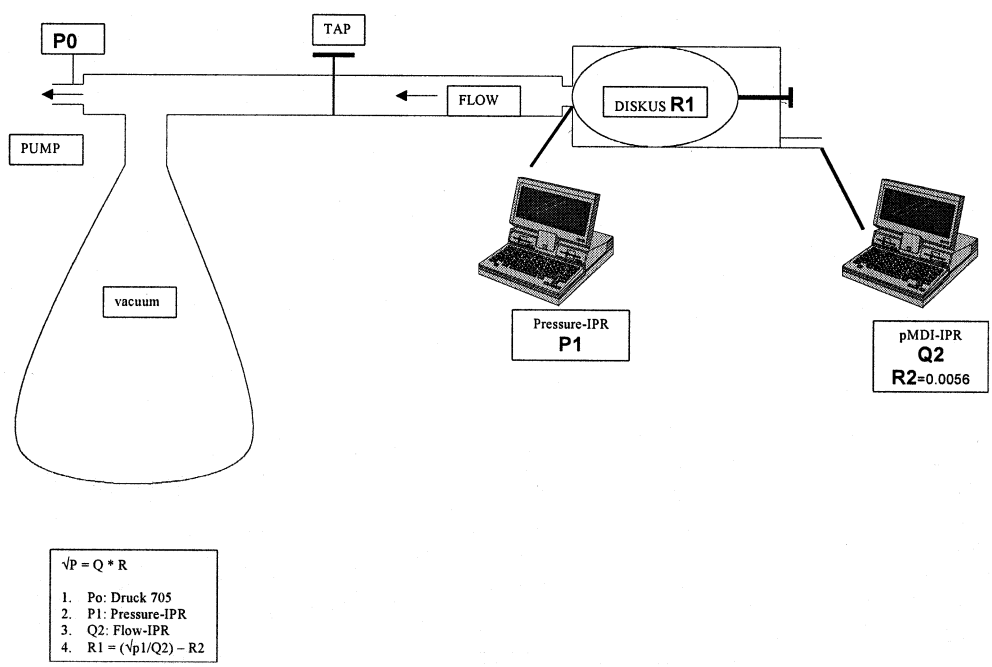

Fig. 1. Study design.

Table 1
The mean resistivities of the PlcD, PwD and the EBD

Diskus® 1–10	*R* PlcD $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$	*R* PwD $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$	*R* EBD $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$
Mean (SD)	0.0215 (6.53e−4) [a,b]	0.0211 (7.87e−4)	0.0211 (7.73e−4)
Range	0.02006–0.02250	0.01963–0.02288	0.01947–0.02286

R PlcD, resistivity of 10 empty placebo Diskussen $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$; *R* PwD, resistivity of 10 Diskussen which contain a strip with blisters filled with powder $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$; *R* EBD, resistivity of 10 Diskussen filled with an empty blister $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$.

[a] Indicates a significant difference between *R* PlcD and *R* PwD.

[b] Indicates a significant difference between *R* PlcD and *R* EBD ($P<0.05$).

Profiles were stored into an IBM computer (Pressure-IPR) (Fig. 1). A flow-measuring device (total resistivity ($R2$) 0.0056 $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$) which allowed measurement of flow ($Q2$) was fixed at the back of the box. The Flow-Profiles through the Diskus® inhaler were also stored into an IBM computer (Flow-IPR).

An 8-l reservoir was connected with a vacuum pump and a Digital Pressure Indicator (Druck 705, Groby, UK). A tap was placed between the box and reservoir.

A negative pressure of -6.0 kPa was created in the reservoir, by using the pump. Then the tap was opened, generating a flow through the Diskus® inhaler simulating an inspiratory effort by inhaling patients. A Pressure-Profile (pressure vs. time curve) and a Flow-Profile were recorded.

Ten placebo and ten Diskus® inhalers containing 200 μg of salbutamol sulphate in 12.5 mg of lactose (Ventolin®, GlaxoSmithKline BV Zeist, The Netherlands) were measured.

Twelve Pressure- and Flow-Profiles of blister-numbers 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5 and 1 were recorded from every inhaler with Ventolin® filled blisters (PwD). After each inhalation through a powder-filled blister, a second inhalation was performed through the empty blisters of each Diskus® inhaler (EBD). Finally, 12 inhalations were made through each placebo Diskus® inhaler that contained no blister at all (PlcD).

3. Analysis

Of each placebo Diskus®, powder filled blister and empty blister of the ventolin® Diskus® inhaler, the resistivity was calculated by (Clark and Hollingworth, 1993),

$$\mathrm{RDiskus} = (\sqrt{P1/Q2}) - R2$$

RDiskus, resistivity of the Diskus® inhaler locked in the box; $P1$, peak pressure drop measured by the Pressure-IPR at the mouthpiece; $Q2$, peak inspiratory flow rate measured by the flow-IPR; $R2$, resistivity of the flow-meter at the back of the box (0.0056 $(kPa)^{0.5}$ $(l\ min^{-1})^{-1}$).

The paired t-test was used to compare the resistivities of the PlcD with the PwD and with the resistivities of the EBD. The resistivities of the PwD and the resistivities of the EBD were also compared. Data were expressed as mean ± standard deviation. A P-value <0.05 was considered significant.

4. Results

Table 1 shows the mean resistivities of the PlcD, PwD and the EBD.

The resistivity of the placebo Diskus® inhaler was slightly but significantly higher than both blisters filled inhalers (with and without powder).

5. Discussion

The aim of this study was to compare the resistivity of an empty placebo Diskus® (PlcD)

and a Diskus® with blisters (powder filled or empty). Significant higher resistivities were found in the placebo Diskus® as compared to the Diskus® that contained blisters (either full or empty). However, this difference, being only 2% of the absolute value, can hardly be expected to have any clinical relevance. No difference in resistivity was found between the ventolin filled blister and the empty blister.

It is not clear from this study why the placebo Diskus® had this slightly higher resistivity.

Small, but not significant differences were found between the several Diskus inhalers. No differences were found between the separate blisternumbers.

Several authors calculated the Diskus resistivity: de Boer (1999) found $\text{Rdiskus} = 0.033\ (\text{kPa})^{0.5}\ (\text{l min}^{-1})^{-1}$ ($= 63\ \text{Pa}^{0.5}\ \text{s l}^{-1}$), wheras Srichana et al. (1998) found $\text{RDiskus} = 0.04\ (\text{kPa})^{0.5}\ (\text{l min}^{-1})^{-1}$ ($= 8.3\ \text{mbar}^{0.5}\ \text{l min}^{-1}$). GlaxoSmithKline R&D found with an in-line flow meter $\text{Rdiskus} = 0.02133\ (\text{kPa})^{0.5}\ (\text{l min}^{-1})^{-1}$ (unpublished data).

The values of resistivity found in our study were lower than in the presented studies, possibly due to the different methodology employed.

In conclusion, patients who are capable of generating sufficient flow through a placebo Diskus® will surely be capable of generating equivalent flows through a Diskus® inhaler containing active drug substance.

Acknowledgements

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