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Peak inspiratory flow rate and slope of the inhalation profiles in dry powder inhalers

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Peak inspiratory flow rate and slope of the inhalation profiles in dry powder inhalers. M.E.A.C. Broeders, J. Molema, N.A. Vermue, H.Th.M. Folgering. ©ERS Journals Ltd 2001.

ABSTRACT: Aerosol delivery depends on device design and inhalation technique. *In vitro* device evaluations have shown that the emitted dose and fine particle mass of dry powder inhalers (DPIs) increase at high peak inspiratory flow rates (PIFR). Since the PIFR is mostly achieved after the release of the powder, slope of the pressure profile is also described as an important determinant. The aim of the present study was to assess whether the PIFR while using Diskus® and Turbuhaler® inhalers could be used to predict the slope of the inhalation pressure profile.

In a group of 10 stable asthma patients and three groups (mild, moderate and severe) of 16 chronic obstructive pulmonary disease (COPD) patients, lung function was measured, and for each device, 18 inhalation profiles were recorded with the inhalation profile recorder during six sessions over 10 weeks.

The values for the pressure slope and PIFR of both Diskus® and Turbuhaler® were significantly correlated. The r-values were 0.865 and 0.882, respectively ($p<0.01$). Percentage explained variance was 74.8% for Diskus® and 77.8% for Turbuhaler®.

Significant correlations were found between peak inspiratory flow rates and slopes. It has been shown for two different dry powder inhalers that peak inspiratory flow rate and slope correlate well in a wide range of patient groups.

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Drug delivery by dry powder inhalers (DPIs) depends on the inbuilt resistance of the inhaler and the inspiratory flow generated by the patient. This inspiratory flow depends on the respiratory muscle force and the airway resistance of the patient [1, 2]. 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 [3]. Inhalation through a DPI is often described by a pressure or flow *versus* time curve (inhalation profile). The pressure profile can be integrated into a flow profile if the device's resistivity is known [4].

In the present study, two multidose dry powder inhalers were compared: Turbuhaler inhaler® (AstraZeneca, Sweden) and the Diskus inhaler® (GlaxoSmithKline, UK). *In vitro* device evaluations showed that the emitted dose and fine particle mass of the Turbuhaler® (higher resistivity) increase at higher peak inspiratory flow rates (PIFRs) [5, 6], whereas the Diskus® (lower resistivity) provided a more consistent dose delivery, relatively independent of different airflows [6, 7]. However, there was therapeutic equivalence of salbutamol given *via* these devices [8].

The PIFR is the most referred parameter of the inhalation profiles. However, it is not the only characteristic parameter. Since the PIFR is mostly achieved after the release of the powder, the slope of the pressure profile (in $kPa \cdot s^{-1}$) has also been described as an important determinant [6, 9, 10]. The present investigation was undertaken to assess whether the PIFR through a Diskus® and a Turbuhaler® inhaler could be used to predict the slope of the inhalation pressure profile.

Methods and measurements

Ten asthmatics and 48 patients with chronic obstructive pulmonary disease (COPD), according to European Respiratory Society (ERS) criteria [11], participated in the study. The patient characteristics are shown in table 1.

Six identical measurements were performed within 10 weeks in order to measure reproducibility. First, a flow/volume curve was taken with an integrating pneumotachograph (Spiro Analyzer ST-250, Fukuda Sangyo, Japan). Next, patients inhaled 400 µg salbutamol *via* a pressurized metered dose inhaler (pMDI) and a spacer to measure reversibility. After 20 min, routine lung function was performed and maximal inspiratory and expiratory mouth pressures (MIP and MEP, respectively) were measured as described by Wilson *et al.* [12]. The inhalation pressure profiles were recorded by a pressure transducer (GlaxoSmithKline Research and Development Dept, Ware, UK), measuring pressures in the mouthpiece during

Table 1. – Patient characteristics

Parameter	Asthma	Mild COPD	Moderate COPD	Severe COPD
Subjects n	10	16	16	16
Sex M/F	2/8	10/6	9/7	13/3
Age yrs	50.7±12.9	65.2±9.1	64.8±9.5	67.3±6.4
FEV_1 % pred	95.9±6.8	76.1±6.5	58.7±6.3	33.6±8.2
Reversibility %	9.0±7.7	5.1±3.7	7.9±5.8	7.4±6.0
RV L	2.1±0.8	2.3±0.7	2.6±0.7	3.6±1.1
TLC L	6.0±1.9	6.0±1.1	6.3±1.5	7.1±1.4
MIP kPa	8.5±3.2	7.9±2.9	7.9±2.5	7.1±2.7
MIP % pred	118.4±51.0	107.6±38.3	104.5±31.3	96.3±34.3
MEP kPa	6.9±1.8	7.7±6.9	7.5±2.4	8.4±3.4
MEP % pred	71.9±21.5	73.6±27.3	68.8±19.4	72.6±26.2
Smoking: non-/ex-/current	4/5/1	3/11/2	2/10/4	1/9/6

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; M: male; F: female; FEV_1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; % pred: percentage of predicted value.

inhalation through Diskus® and Turbuhaler®. The inhalation profiles were stored on the inhalation profile recorder (IPR). Patients inhaled three times through each device, hence, 18 profiles through each device were collected from each patient during the study. Both devices were blinded in a specially constructed box.

The parameters of the dry powder inhaler-inhalation profile recorder (DPI-IPR) are: 1) pressure slope (Sl) ($kPa \cdot s^{-1}$); 2) peak pressure drop (PPD) (kPa); 3) time to peak pressure drop: the time between the onset of the inhalation and the moment of reaching the PPD (T_P) (s) (the start of the measuring time is the moment that the pressure passes the 0.2 kPa threshold); and 4) PIFR ($L \cdot min^{-1}$). If the PPD was reached within the first 0.5 s, the slope was calculated by PPD/T_P. If the PPD was achieved after 0.5 s, the slope was calculated by pressure at 0.5 s/0.5 s to approach the actual slope. The relationship between PIFR and PPD was calculated by $PPD=(PIFR \times R)^2$ [4], where R is the resistivity of the devices used, measured in a separate experiment ($R_{Diskus®}=0.02133\ kPa^{0.5} \cdot L^{-1} \cdot min$ and $R_{Turbuhaler®}=0.03223\ kPa^{0.5} \cdot L^{-1} \cdot min$) [13].

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Statistical analysis

The means of slope and PPD of the 18 inhalation profiles were calculated for each patient. Also the mean lung function parameters were calculated. Relationships between slopes and PIFRs of all profiles of the Diskus® (Sl_D and $PIFR_D$) and slopes and PIFRs of all profiles of the Turbuhaler® (Sl_T and $PIFR_T$) were calculated using Spearman's correlation coefficient. The correlations between the maximal inspiratory pressure slope and PIFR for Diskus® and Turbuhaler® were again calculated using Spearman's correlation analysis. Data were expressed as mean±SD. A p-value <0.05 was considered statistically significant.

Results

No significant difference was found between Sl_D and Sl_T (13.5±5.0 and 13.8±4.7 $kPa \cdot s^{-1}$, respectively). However, PIFR values of both devices were significantly different ($PIFR_D$ 108.3±20.4 and $PIFR_T$ 76.1±13.8 $L \cdot min^{-1}$; $p<0.001$), due to the different resistivities of the devices.

The values of the slope and PIFR of both Diskus® and Turbuhaler® devices were significantly correlated. The r-values were 0.865 and 0.882, respectively ($p<0.01$). Figures 1 and 2 show the correlation of slope and PIFR of Diskus® and Turbuhaler®. The percentages of explained variance ($r^2 \times 100$) were 74.8% and 77.8%. Furthermore, significant correlations were found between the maximal inspiratory mouth pressure, slope and PIFR. The r-values were 0.449 for MIP *versus* Sl_D and 0.571 for MIP *versus* $PIFR_D$. The r-value for correlation between MIP *versus* Sl_T was 0.484, and for MIP *versus* $PIFR_T$ was 0.632 ($p<0.01$).

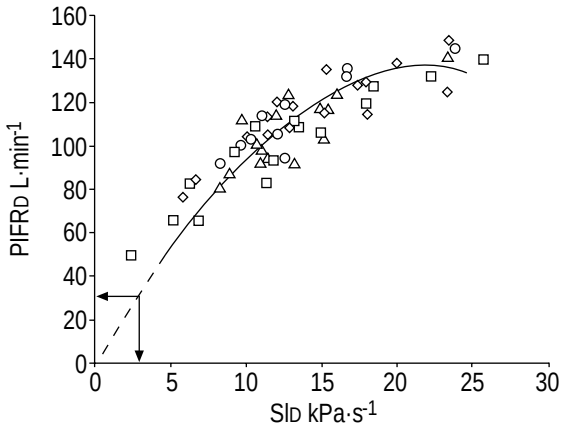

Fig. 1. – Correlation of slope (Sl_D) and peak inspiratory flow rate ($PIFR_D$) of Diskus®. Data were extrapolated. Arrows refer to the relationship between the minimal $PIFR_D$ (30 $L \cdot min^{-1}$) and the accompanying Sl_D. □: severe; △: moderate; ◇: mild; ○: asthma. r=0.865.

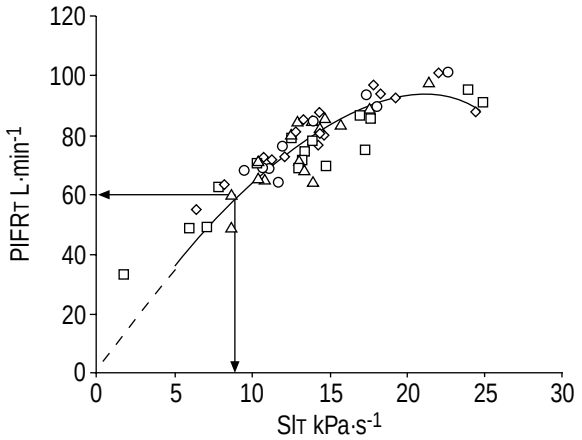

Fig. 2. – Correlation of slope (SlT) and peak inspiratory flow rate (PIFRT) of Turbuhaler®. Data were extrapolated. Arrows refer to the relationship between the minimal PIFRT (60 $L \cdot min^{-1}$) and the accompanying SlT. □: severe; △: moderate; ◇: mild; ○: asthma. r=0.882.

Discussion

The aim of present study was to assess whether the PIFR through Diskus® and Turbuhaler® inhalers could be used to predict the slope of the inhalation pressure profile. This study showed significant correlations between the PIFR and pressure slope of the inhalation irofiles of the two inhalers.

Drug particle release from DPIs is determined by a patient's peak inspiratory flow rate and pressure slope. Both depend on the patient's effort, related to the peak flow and the pressure build-up during the first part of the inhalation profile. The significant correlations between the maximal inspiratory mouth pressure and the inhalation profile parameters were in agreement with this principle. Therefore, it is important that patients should be instructed to inhale in a fast and powerful fashion.

Respiratory muscle function is often decreased in COPD patients due to hyperinflation, hypoxaemia and the use of corticosteriods. It must be noted that even the severe COPD patients in this study generated almost normal MIP values (96.3% of predicted). Nevertheless, their MIP values were considerably lower than the values of the asthmatics and the other COPD patients. Oral corticosteroids were not used, so hyperinflation must play a role. Although it is apparent that the PIFR and slope parameters are important determinants for an efficient use of a DPI (*e.g.* drug deposition), the results of this study indicate that they are also related to each other ($r=0.865$ ($p<0.05$) for the Diskus® and $r=0.882$ ($p<0.05$) for the Turbuhaler®). The significant correlation between PIFR and the pressure slope in this study may indicate that the measured PIFR will be a reasonable representation of slope. However, for a given PIFR, the slope can have a wide range (*e.g.* where PIFRD=120 $L \cdot min^{-1}$, SlD varied between 13 and 24 $kPa \cdot s^{-1}$; fig. 1).

It is remarkable that such good linear correlations were found in these systems, which are by definition alinear, due to the turbulent flows (Rohrer equation: $P=k_1 \times Q^2+k_2 \times Q$). The devices are designed to generate turbulence at the mouthpiece in order to achieve optimal aerosolization of the drug [10, 14]. However, the function is not a linear one over the entire range: the line was fitted through zero flow at zero slope. Comparing both parameters in different studies should be done with some caution. No significant difference between slopes of Diskus® and Turbuhaler® were found. However, a decreasing slope by increasing resistivity could be expected. This may possibly be due to the small difference in the manufacturers' instructions. The Turbuhaler® instructions emphasize to inhale deeply and forcefully; whereas the instructions of the Diskus® emphasizes inhaling deeply and forcefully, but not too fast. It is possible that patients inhaled with less effort through the Diskus®, resulting in a lower slope value. Eventually a high effort through a high resistivity device (Turbuhaler®) resulted the same slope as a "not too fast effort" in a lower resistivity device (Diskus®). In the literature, only PIFR-values have been shown, and minimal attention has been paid to other inhalation profile parameters. However, since the slope is such an important parameter, there must be a minimal slope for "optimal" delivery. Extrapolation of the present data gave a slope value of 3 $kPa \cdot s^{-1}$ for Diskus® at a PIFR of 30 $L \cdot min^{-1}$, (although these extrapolated values were outside the measured range) and 9 $kPa \cdot s^{-1}$ for Turbuhaler® at PIFR of 60 $L \cdot min^{-1}$.

In conclusion, reasonable correlations were found between peak inspiratory flow rates and slopes. It has been shown, for two different dry powder inhalers, that peak inspiratory flow rate and slope correlate well in a wide range of patient groups.

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