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The effect of the inhalation flow on the performance of a dry powder inhalation system

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Dry powder inhalation systems are mostly composed of complexes of (lactose)carriers and micronised drug crystals. These complexes are separated during inhalation of the powder in order to deliver respirable particles to the lungs: this process is energy-dependent. The effect of increasing inhalation flows was investigated both in vitro and in vivo. In vitro it was found that only particles > 5 μm separated better with increasing flows. Particles < 5 μm were separated completely at low flows. In vivo no significant differences in bronchodilation (FEV_1 and MEF_{50}) after inhalation at 40 or 80 l/min were found. This means that patients can use dry powder inhalers with low inhalation flows, which is beneficial to those patients with reduced muscle power.

Introduction

Most inhalation powders consist of micronised drug crystals in small quantities and an excipient added to prevent aggregation of these small crystals and to increase the volume (Byron, 1986). The drug crystals are supposed to bind to the larger excipient crystals in a so-called ordered mixture, thus inhibiting segregation of the mixture (Cartilier and Moes, 1986). The excipient-drug complexes are too large to reach the airways of the lungs effectively and should therefore be split into separate components by means of nebulization of the powder in the air inhaled by the patient (Byron, 1987). Air whirls from the turbulent flow through the inhaler cause this separation to be realized. In contrast to the metered-dose inhalers, the dry-powder inhalation system allows the patient to influence the complex diameter and thus the distribution of the inhaled material in the lungs. If the patient inhales with a low flow, the efficacy of the separation process will decrease. Many patients, especially children, are unable to generate high inhalation flows (Pedersen, 1986). The present study describes the in vitro and in vivo behaviour of an inhalation

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powder at various flow levels, and the degree of bronchodilatation resulting from inhalation at these flow levels.

Materials and Methods

In vitro

The diameter of a complex or particle in an inhalation powder can be determined by having the powder to be 'inhaled' through an impactor. An impactor has the capacity to separate the inhalation powder in a number of fractions, the aerodynamic diameter of the particles being the determinant factor (Martin et al., 1968). In this study a Pilat Mark 3-impactor (Pollution Control Systems Corp.) with five compartments was used. The impactor was furnished with a pre-separator, in order to collect the very large complexes. This prevents the overloading of the first compartment, which would cause an unwanted change in the cut-off point. All interior surfaces of the impactor and the pre-separator were lined with a thin layer consisting of a mixture of polyethylene glycol/polysorbate, in order to prevent bouncing. A Cyclohaler, containing a capsule holding 400 μg salbutamol (Salbutamol Cyclocaps, Pharbita batch no. 015088) was placed on the pre-separator. Then the capsule was punctured and air was sucked through the entire system by a vacuum pump. The investigation was carried out at air flows of 40, 60 and 80 l/min, respectively, over a time period of 30 s duration.

The cut-off points (μm) of the various stages of the Pilat impactor were:

	stage 1	stage 2	stage 3	stage 4	stage 5
at 40 l/min	9.8	7.3	2.8	1.40	0.75
at 60 l/min	8.0	6.1	2.3	1.15	0.61
at 80 l/min	6.9	5.3	2.0	0.96	0.52

The mass of salbutamol in the inhaler, in the pre-separator and in each impactor stage was determined by HPLC analysis.

The amount of salbutamol consisting of complexes < 7, < 5 and < 3 μm was then calculated (with reference to the total capsule contents). In addition, this was done in a similar manner with reference to the total amount in the impactor in order to calculate the mass median aerodynamic diameter (Chowhan et al., 1991). The results are expressed as a percentage ($\pm$S.D., $n = 5$). Statistical evaluation was carried out by means of one-way analysis of variance. In the evaluation a level of significance of $\alpha = 0.05$ was observed.

In vivo

For the in vivo part of the study, 16 stable asthma patients were selected. These patients were all attending the pulmonology outpatient clinic of the Slotervaartziekenhuis. The group consisted of five men and 11 women, the baseline FEV_1 was between 50 and 70% of the predicted value and all exhibited an improvement of $> 15\%$ after inhalation of a bronchodilator. The age of the patients was 42 ± 13.9 years. Informed consent was given in writing and the Medical Ethical Committee of the hospital approved the study. The patients were trained to inhale one vital capacity breath with inhalation flows of 40 and 80 l/min through the inhalation system. The inhalation flow was measured with a Fleisch pneumotachograph connected to the inhaler. The patients could read the flow level from an oscilloscope. The test preparations (from the same batches as those in the in vitro experiment) were administered double-blind, double-dummy, cross-over and randomized. The FEV_1 was allowed to deviate $< 15\%$ on the second test day.

After inhalation of the two preparations the FEV_1 and the MEF_{50} were measured at $t = +15$, $+30$, $+60$ and $+120$ min by means of a spirometer system (Jaeger Masterlab). The highest of three measurements of each series was selected. All values were determined by means of three-way analysis of variance. The residual error was subsequently used to calculate the 90% (shortest) confidence intervals of the ratio of the means (Schuirmann, 1987).

Results

In vitro

The amounts of salbutamol (as a percentage of the capsule contents) remaining in the inhaler or

TABLE 1

Amount of salbutamol (percentage ± S.D.) remaining in the inhaler and impacted in pre-separator

Flow (l/min)	Inhaler	Pre-separator
40	12.8 ± 1.6	46.3 ± 6.6
60	13.8 ± 2.3	41.0 ± 3.8
80	11.8 ± 1.8	40.3 ± 2.5
	$p = 0.3$	$p = 0.12$

TABLE 2

Amount of salbutamol (percentage ± S.D.) in crystals < 7, < 5 and < 3 μm at 40, 60 and 80 l/min

Flow (l/min)	< 7 μm	< 5 μm	< 3 μm
40	25.4 ± 3.7	23.0 ± 3.5	19.7 ± 3.7
60	32.4 ± 2.3	24.6 ± 1.7	21.6 ± 1.7
80	40.6 ± 2.3	26.4 ± 1.7	22.4 ± 1.3
	$p < 0.01$	$p = 0.12$	$p = 0.25$

TABLE 3

Amount of salbutamol (percentage ± S.D.) in crystals < 7, < 5, < 3 μm and the MMAD (μm) at 40, 60 and 80 l/min

Flow (l/min)	< 7 μm	< 5 μm	< 3 μm	MMAD (μm)
40	52.8 ± 10.3	41.2 ± 9.4	25.0 ± 7.8	7.2 ± 1.5
60	59.8 ± 4.6	46.0 ± 3.7	32.2 ± 2.8	5.8 ± 2.8
80	68.0 ± 3.2	49.2 ± 2.7	32.4 ± 3.3	5.3 ± 0.4
	$p < 0.01$	$p = 0.15$	$p = 0.07$	$p = 0.02$

deposited in the pre-separator are listed in Table 1, those in crystals < 7, < 5 and < 3 μm being collected in Table 2.

There was no statistically significant difference in the amount of salbutamol leaving the inhaler. Any variations that might occur between the salbutamol masses deposited in the pre-separator and the impactor cannot be ascribed to differences in emptying of the inhaler.

No significant difference was found between the respective masses of salbutamol < 5 and < 3 μm, whereas that of < 7 μm clearly deviated. Calculation of the least significant difference leads to the conclusion that the differences between the masses are significant at all flow levels.

This implies that the mass of salbutamol with a complex diameter > 5 μm increases with rising flow levels.

The amounts of salbutamol as a percentage of the mass in the impactor in crystals < 7, < 5 and < 3 μm and the values of the mass median aerodynamic diameter (MMAD) are summarized in Table 3.

The 'gain' achieved by inhalation at higher flow levels is reflected by the increased amount of complexes with a larger diameter. The median diameter decreased considerably. However, the increase was greatest in the case where the flow rose from 40 l/min to 60 l/min.

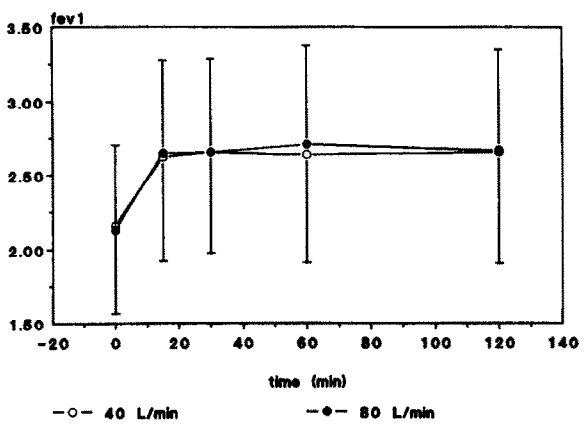

Fig. 1. Improvement in FEV_1 (mean, S.D.) after inhaling a salbutamol/lactose blend at flows of 40 and 80 l/min.

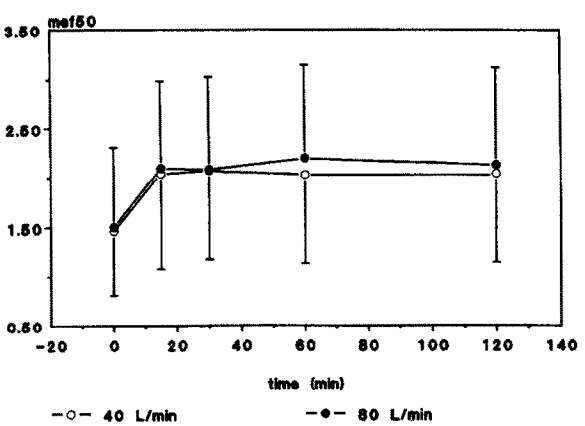

Fig. 2. Improvement in MEF_{50} (mean, S.D.) after inhaling a salbutamol/lactose blend at flows of 40 and 80 l/min.

TABLE 4

Confidence intervals of the ratio of the means of FEV_1 and MEF_{50}

	FEV_1	MEF_{50}
$t = +15$ min	96–102%	93–102%
$t = +30$ min	97–103%	94–105%
$t = +60$ min	95–100%	88–97%
$t = +120$ min	96–103%	90–102%
Maximum value	97–103%	94–102%

In vivo

The patients inhaled 40.6 ± 3.5 l/min during the 40 l/min session and 77.3 ± 11.4 l/min during that of 80 l/min ($p < 0.05$). The baseline FEV_1 values were 2.16 ± 0.6 and 2.1 ± 0.6 l ($p = 0.61$), the baseline MEF_{50} values being 1.46 ± 0.65 and 1.5 ± 0.8 l/s, respectively ($p = 0.72$). The course of change of the lung function parameters is depicted in Figs 1 and 2. The analysis of variance of the FEV_1 for individual time points demonstrated that no significant differences were obtained. In addition, the 90% confidence intervals were all found to be within the 80–120% interval (regarded by the FDA as the interval justifying the claim of equivalence). The same applies for the MEF_{50}, with the exception of the values at $t = +60$ min (see Table 4). At that time point, the MEF_{50} after inhalation at 40 l/min was 2.03 ± 0.9 l/s; after 80 l/min it was 2.2 ± 0.95 l/s. This (small) difference was significant, the 90% confidence interval being 88–97%, with the ratio of the means amounting to 92.3%. The maximum value of the FEV_1 was 2.73 ± 0.73 and 2.74 ± 0.66 l, respectively; for the MEF_{50} this was found to be 2.22 ± 0.97 and 2.26 ± 0.93 l/s, respectively. Analysis of variance did not exhibit differences, whereas the 90% confidence intervals were within the 80–120% interval.

Discussion

The results of the in vitro part of the study demonstrate that increasing inhalation flow is accompanied by greater separation of the complex. With rising flow, the amount of salbutamol in the pre-separator decreases: this indicates that the diameter of the complex decreases more rapidly than the cut-off point of the pre-separator. For a dry-powder inhaler, such as the Cyclohaler, high inhalation flow is not detrimental, whereas for metered-dose inhalers it has been reported to be disadvantageous (Newman et al., 1981). On the basis of these observations, dry-powder inhalers are generally recommended to be used at high inhalation flows.

Increasing flows change the amount of salbutamol < 5 and < 3 μm only to a limited extent, in contrast to the case of salbutamol < 7 μm. The raw material used in the manufacturing of this batch contains the same percentage of the fraction < 5 μm as observed here. This implies that the fraction < 5 μm has been fully separated from its carrier.

The above data suggest a dichotomous mechanism of separation over the range of flows employed in the present study. The assumption is made that binding between all drug and excipient crystals reaches completion. The degree of separation between drug and excipient crystals is determined by the energy supplied to the system by means of air passing through the inhaler. Therefore, a relationship exists between the degree of separation and the inhalation flow.

On the basis of theories concerning the binding between crystals, it is expected that the largest crystals of drug will separate first as a result of having a greater momentum (Stewart, 1986). However, the experimental findings demonstrated that the most readily separated crystals were those of smaller size. An explanation for this can be found in the experiments reported by Staniforth et al. (1981, 1982). Their experimental results demonstrate that in a powder composed of a relatively large vehicle with smaller crystals bound to the surface, there may exist a weakly bound fraction, which increases with increasing concentrations of the smaller bound crystal. In addition, a relationship exists with the diameter of the carrier crystals; separation occurs faster when the carrier crystals are smaller. The experiment discussed here confirms the observations of Staniforth et al. and provides the additional finding that the non-bound or weakly bound fraction

consists of small crystals. Elaborating on this finding, one may speculate as to whether the small crystals are bound at all.

However, the requirement of vigorous inhalation cannot be discarded because the availability of the salbutamol is flow-dependent. Nevertheless, the in vivo part of this study has clearly demonstrated that increasing availability is not expressed in stronger bronchodilation. At all measuring points, with a single exception, the degree of dilatation remains at the same level, the exception being of little significance clinically. An explanation for the increase in availability not being reflected in stronger dilatation cannot be put forward with certainty. The mass of salbutamol at 40 l/min may already be so large that maximum dilatation is reached; another possibility, since the gain is particularly due to the larger particles, is that these particles do not reach the receptor. The rise in concentration at the receptor site is insufficient. We refer to the view of Newman (1985), according to whom the respirable fraction of an inhalation preparation consists of crystals < 5 μm. At any rate, the requirement for vigorous inhalation can be excluded.

The present study has clearly demonstrated that in vitro data, resulting from impactor testing, cannot be extrapolated to the in vivo situation. In this respect, it should be borne in mind that the impactor is capable of detecting differences that are so small as to be clinically irrelevant. Conversely, it can be assumed that, if no differences are demonstrated during the impactor study on various preparations containing identical active ingredients, clinical testing for therapeutic equivalence is superfluous. Currently, it remains unknown as to what in vitro differences are still acceptable or are expressed in a clinically relevant difference. On consideration of the results presented in this study, it can be assumed that substantial in vitro differences may be acceptable.

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