Pulmonary Deposition and Clinical Response of ^{99m}Tc-Labelled Salbutamol Delivered from a Novel Multiple Dose Powder Inhaler

Mika Vidgren,[1,5] Jukka Arppe,[1] Petra Vidgren,[2] Liisa Hyvärinen,[3] Pauli Vainio,[4] Matti Silvasti,[2] and Hannu Tukiainen[3]

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Pulmonary deposition of ^{99m}Tc-labelled sulbutamol was determined after delivery from a novel multiple dose powder inhaler (Easyhaler®). The clinical efficacy of the inhalation powder, evaluated simultaneously with gamma camera detection, was compared with that obtained after drug delivery from a metered dose inhaler-spacer combination. The study was performed as an open, non-randomized cross-over trial. A single dose of radiolabelled inhalation powder was inhaled on the first and the inhalation aerosol, as control, on the second study day. Sulbutamol sulphate was labelled with ^{99m}technetium, and the inhalation powder was formulated by mixing radioactive drug particles with carrier material. Aerodynamic properties of the radiolabelled inhalation powder were similar to those of the unlabelled salbutamol powder. Delivered dose from the breath-actuated powder inhaler was adjusted to be equal to two puffs from a conventional aerosol actuator with a short plastic mouthpiece. Twelve non-smoking asthmatic patients participated in the trial. The mean pulmonary deposition of 24% was obtained after drug delivery from Easyhaler® powder inhaler. Clinical efficacy of the medications was similar in terms of area under the FEV_1 curve, maximum FEV_1 and the improvement ratio. Thus it can be suggested that powder delivery from Easyhaler® powder inhaler and the aerosol delivery through the spacer are equally effective.

KEY WORDS: inhalation powder; gamma scintigraphy; pulmonary deposition; bronchodilation.

INTRODUCTION

Breath-actuated dry powder inhalers were initially developed to avoid coordination problems of drug delivery with metered dose inhalers (MDIs) (1). Besides dosing difficulties another drawback of MDIs is their chloronated hydrocarbon propellant content as these compounds deplete the ozone layer (2). Further, the cold Freon effect of the evaporating propellants can irritate the hyperreactive airways of asthmatic patients (3). Therefore, alternative drug delivery systems to the MDIs should be established.

Inhalation powder is an alternative drug delivery system in the treatment of bronchial asthma. Traditionally, inhalation powder is packed in hard gelatin capsules, whose handling can require complex maneuvers. Capsules have to be inserted in powder devices and the drug powder has to be released using various kinds of techniques. Patients suffering from an acute asthma attack or with decreased manual skills have found usage of traditional single dose powder inhalers difficult and time-consuming (4). Thus, multiple dose powder inhalers (MDPIs) preloaded with several doses of active drug are more reliable, easier and more convenient to use.

Radiotracers can be used to investigate distribution of inhaled drug particles in the human respiratory tract (5–7). Both non-medical and real drug particles can be labelled to study their deposition after delivery from inhalation dosage forms (7–9). Deposition patterns in the human airways have been assessed after inhaling the medication from MDIs and dry powder inhalers (10–12). The labelling methodology is based on either chemical of physical incorporation of a radiotracer in observed particles (13,14). However, inhaled drug substances are most often labelled by physically including a radioactive compound in the formulation, because the molecular structure of inhaled drugs is seldom suitable for chemical incorporation of γ-emitters.

The aim of this study was to assess the deposition pattern of inhaled salbutamol sulphate delivered from a novel multiple dose powder inhaler (Easyhaler®) in asthmatic patients. In addition, clinical efficacy of the inhalation powder as well as that of a corresponding dose of salbutamol delivered from an MDI-spacer combination were investigated by using flow volume spirometry.

MATERIALS AND METHODS

Study design

The study was performed as an open, non-randomized cross-over trial, in which the radiolabelled compound was given on the first and the control treatment on the second study day.

Study preparations

The deposition of inhaled salbutamol sulphate particles was investigated after administration of the drug from a novel multiple dose powder inhaler (Easyhaler®, Orion-Farmos pharmaceuticals, Espoo, Finland). The clinical response after Easyhaler® delivery was compared with that of a MDI-spacer combination (Ventoline® 0.1 mg/dose MDI with Volumatic® spacer, Glaxo Pharmaceuticals, UK). The delivered dose of salbutamol dry powder (0.18 mg) was adjusted to be equal to two puffs from an 0.1 mg/dose MDI. Because on average 10% of the aerosol dose retained in the actuator, patients inhaled also 0.18 mg of salbutamol from two puffs from an MDI.

The MDI was chosen for the reference dosage form, because it is commonly used in the inhalation therapy of asthma. The investigated multiple dose powder inhaler, Easyhaler®, was developed to be an alternative drug delivery system to the conventional MDI (Fig. 1). The dose regimen of the Easyhaler® is such that one delivered dose from the powder device is adjusted to be equal to two delivered doses

[1] Department of Pharmaceutical Technology, University of Kuopio P.O. BOX 1627, FIN-70211 Kuopio, Finland.

[2] Orion-Farmos pharmaceuticals, P.O. BOX 1780, FIN-70701, Kuopio, Finland. Departments of [3]Pulmonary Diseases and [4]Clinical Physiology Kuopio University Hospital, FIN-70210 Kuopio, Finland.

[5] To whom correspondence should be addressed.

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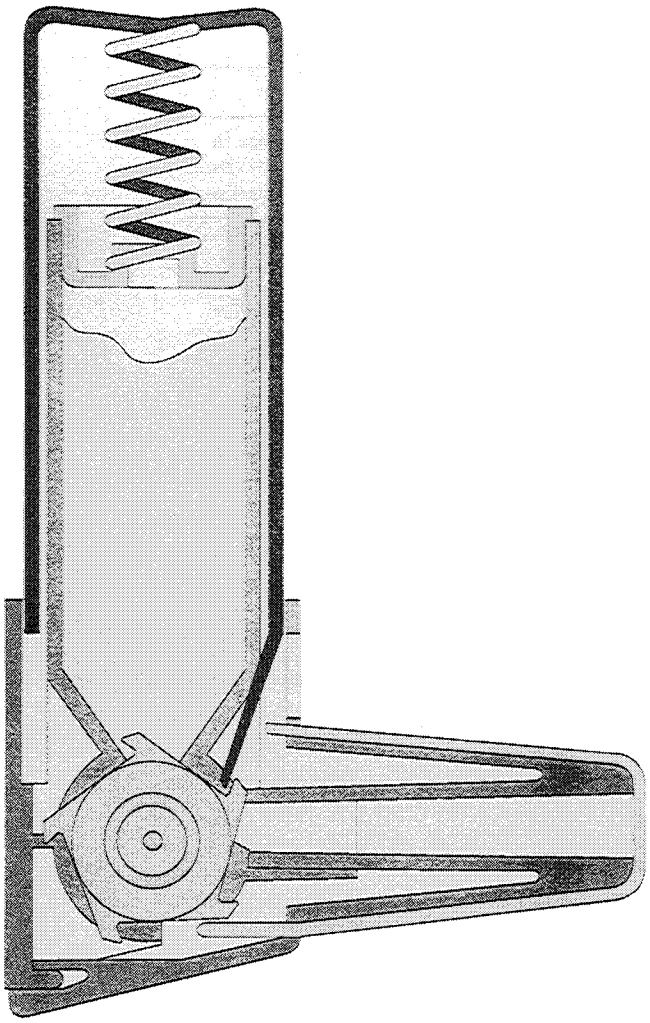

Fig. 1. Cross section of the novel multiple dose powder inhaler (Easyhaler®).

from the MDI. Thus, for obtaining similar topical effects in the airways equal pulmonary deposition should be achieved. Volumatic® large volume spacer device was combined to the MDI in order to eliminate coordination problems in the delivery of the reference drug and to optimize the pulmonary deposition of the MDI delivery.

Labelling procedure

The labelling procedure was performed as described by Arppe and Vidgren (15). Briefly, ^{99m}technetium (^{99m}Tc) was eluted as a pertechnetate from a radionuclide generator, and placed in a glass tube. One drop of ammonia and one drop of 5% tetraphenylarsonium chloride in water solution was added. The radioactivity was transited to the organic solvent by shaking the water solution with 3 ml of chloroform. Finally, the organic phase was filtered through a silicone-treated phase-separating filter paper. The filtrate contained about 60% of the original activity in a form of tetraphenylarsonium pertechnetate.

Salbutamol sulphate was suspended in the chloroform phase and homogenized. The suspension was sprayed to a hot air stream and the dried drug particles were collected to a filter. The inhalation powder was prepared by mixing the radioactive drug particles and lactose of inhalation grade (Ph. Eur.). Three powder batches were used during the gamma scintigraphic study (S03, S04, SO5). The mean activity of the drug dose was 4.8 MBq.

Patient characteristics

Twelve asthmatic patients, seven males and five females, participated in the study. Their mean age was 52 years (range 41–61 years), the mean height was 169 cm (range 160–180 cm), and the mean weight was 72 kg (range 59–92 kg). The duration of asthma ranged from 1 to 15 years (mean 7 years), and the disease was graded mild in three cases, moderate in eight cases and severe in one case. The baseline FEV_1 (mean ± SD) of the predicted value was 76 ± 24% before the powder delivery and 72 ± 21% before the aerosol delivery (Table I). Individual variation of the FEV_1 values between the two study days was less than 15%. Improvement in the FEV_1 or PEF over 15% after inhalation of 200 μg of salbutamol from an MDI was shown within two weeks before the study. The patients were free of respiratory infections within 6 weeks before the study. They also abstained from controlled-release theophylline preparations for at least 48 hours, from oral sympathomimetics for at least 12 hours, and from all inhaled drugs for at least 8 hours. Other asthma and allergy medication, except oral steroids, were stopped 8 hours before the study, and the treatment of concomitant diseases were kept unchanged during the study.

Drug delivery

In order to document mode of inhalations, Easyhaler® powder device was inserted in a specially designed cover, which was connected to the pneumotachograph, from which the signals of the air flow units (l/min) were detected during inhalations (16). The patients were instructed to exhale normally, place the mouthpiece tightly between the lips, inhale rapidly and deeply to the total lung capacity (TLC), hold the breath for about ten seconds, and exhale normally. When the aerosol doses were inhaled, the aerosol canister was first shaken and then connected to the Volumatic® spacer. The patients were then instructed to fire two puffs to the spacer, immediately place the spacer tightly between the lips, inhale slowly to the TLC, hold the breath for about ten seconds, and exhale normally.

Assessment of deposition and efficacy

The deposition patterns of the inhaled drugs were monitored by a large-field gamma camera (Type 400T, General Electric, WI, USA) equipped with a low energy all purpose collimator. The anteroposterior and posteroanterior views of the chest of the subjects were obtained. The same measurement geometry was used for three minutes per view in a supine position. The data was collected to the Gamma-11-system with PDP 11/34 computer (Digital Equipment Corp., MA, USA) with 64 × 64 collection matrix. The results of the deposition data were calculated after the correction of the time decay of ^{99m}Tc, the background radiation and the individual attenuation of the subjects. To obtain individual attenuation coefficients, a flat cobalt source was used. The

Table I. Baseline obstruction rate (baseline FEV_1/predicted value of FEV_1) and pulmonary deposition and bronchodilating effect of the medications. Individual values and mean (SD).

Patient no.	Easyhaler®			MDI with spacer	
	Obstruction rate (%)	Pulmonary deposition (%)	Change in FEV_1 (%) from the baseline	Obstruction rate (%)	Change in FEV_1 (%) from the baseline
1	89	33	12	90	16
2	68	15	29	59	58
3	85	25	9	78	19
4	90	27	7	84	12
5	73	23	13	72	14
6	31	29	33	31	29
7	51	15	36	53	23
8	111	17	6	103	13
9	93	24	21	92	27
10	70	25	20	61	31
11	99	19	17	89	20
12	47	33	36	49	41
Mean	76	24	20	72	25
SD	24	6	11	21	13

radioactivity of the initial drug dose measured from the metering cylinder was considered as 100%. Thus the results were fractionized (%) for the activity in the device, in the upper airways and in the lungs. The means and the standard deviations of the percents describing the deposition areas were calculated.

Spirometric indices were measured in a sitting position on both study days immediately before, and 15, 30 and 60 minutes after the inhalation of the study preparations. The measurements were carried out by flow-volume spirometry (Medikro 202®, Medikro, Kuopio, Finland). At least two acceptable exhalations were performed and the best one was included in the final analysis. The efficacy of the treatments was defined in terms of forced expiratory volume in one second (FEV_1). The primary efficacy variables were area under the FEV_1 curve ($AUCFEV_1$), the maximum FEV_1 value (FEV_1MAX) and the maximum percentual change in the FEV_1 ($FEV_1MAX\%$). In addition, the maximum FEV_1 as a percent of the predicted values were calculated.

Statistical methods

The statistical significance of differences in the lung function measurements were analyzed by the method of analysis of variance for repeated measurements. Two sided p-value less than 0.05 was considered to be statistically significant. Spearman's rank correlation test was performed to evaluate the correlation between the percentual lung deposition and inspiratory parameters and between lung deposition and percentual change in FEV_1 values. Conventional 90% confidence limits for the radio MDPI/MDI of the area under the FEV_1 and maximum FEV_1 values and maximum FEV_1 as a percent of predicted were calculated.

Ethical aspects

The study was approved by the ethical committee of Kuopio University Hospital. All the volunteers gave an informed consent before attending the trial.

RESULTS

Assessment of the radiotracer technique

The cascade impactor study was performed for ensuring that the radioactivity illustrated reliably the deposition of the drug particles (17). In this study modified Andersen 8-Stage Non-Viable Sampler (Andersen Instruments, Inc., Atlanta, Georgia, USA) with an air flow of 28.3 l/min was used. The distribution of the drug particles and radioactivity on different stages of the particle separator are presented in Table II. The results are expressed as two particle size fractions, smaller and larger than 5.8 μm, the latter illustrating the respirable fraction which can be predicted to deposit in the whole lung area of the patients. The figures point out that the distribution of radioactivity within these two particle size fractions was identical to the drug content. Hence the amount of radioactivity detected in the device and in the lungs as well as in the oropharynx reflected the amounts of radiolabelled drug delivered to these sites.

To ensure that the in vitro deposition of the radioactive salbutamol powder was similar to the unlabelled product, and thus the results would also represent untreated products, the deposition of the labelled and unlabelled batches was compared by the cascade impactor. Amounts of untreated and labelled drug recovered from the respirable stages of the cascade impactor (<5.8 μm) are presented in

Table II. Distribution of drug particles and radioactivity on different stages of the Andersen cascade impactor.

Batch	Particle size (%) < 5.8 μm	Activity/Drug <5.8 μm	Activity/Drug >5.8 μm
S03 ^{99m}Tc labelled	29	1.00	1.00
S04 ^{99m}Tc labelled	27	1.00	1.00
S05 ^{99m}Tc labelled	33	1.06	0.98
S02 unlabelled	25	—	—

Table II. In all cases the labelling procedure produced a slightly reduced aerodynamic particle size distribution, with more particles penetrating to the respirable stages of the impactor. This change is, however, at the same range as reported for the similar deposition study (12).

Deposition of the dose in vivo

Data of the mode of inhalation was obtained by spirometer when the Easyhaler® delivery was studied. The mean inhaled volume through Easyhaler® was 2.6 litres ranging from 1.5 to 4.1 litres, and the mean peak inspiratory flow (PIF) was 52 l/min (range 32–65 l/min). On average 32% of the total volume was inhaled during the first second.

The amount of activity retained in the dry powder inhaler was (mean ± SD) 6 ± 2% (Fig. 2). Thus the amount was relatively small being at the same range as usually retained in a conventional aerosol actuator with a short plastic mouthpiece. The fractional amount of the dose deposited in the upper airways ranged from 62 to 79% of the total dose the mean being 71 ± 6% (Fig. 2). The amount of activity detected in the lungs of the asthmatic patients was between 15% and 33% of the total dose. The mean of this fraction was 24 ± 6% (Fig. 2, Table I).

There was no significant correlation between the inspiratory parameters and the percentual lung deposition. Neither was there a correlation between the lung deposition and maximum percentual change from the baseline in FEV_1 or the rate of obstruction (FEV_1 in baseline/predicted value of $FEV_1 \times 100$). The individual measurements are presented in Table I.

Lung function measurements

There were no statistically significant differences between the treatments in lung function parameters after the administration of doses tested (Fig. 3 and Table III). The maximum FEV_1 was 3.0 litres after both treatments. The area under the FEV_1 curve was 174 after Easyhaler® and 174 after MDI with spacer. The maximum percentual change in FEV_1 was 20 and 27% after the powder and the aerosol delivery, respectively. The maximum FEV_1 values as a percent of the predicted were 89% for the Easyhaler® and 88% for the MDI-spacer combination (Table III).

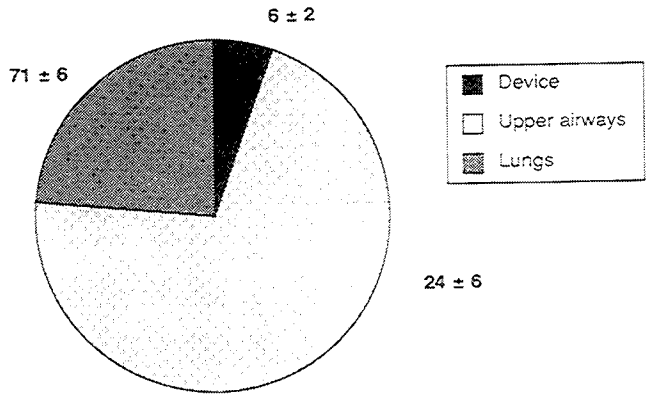

Fig. 2. Fractional deposition (mean ± SD) of ^{99m}Tc-labelled salbutamol sulphate in 12 asthmatic patients after drug delivery from Easyhaler®.

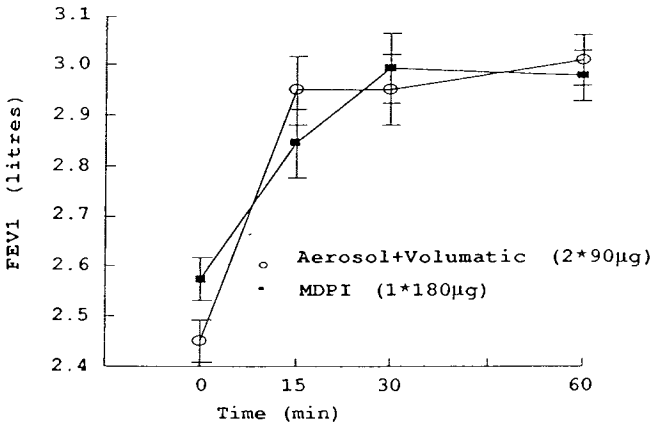

Fig. 3. Absolute values of the forced expiratory volume (FEV_1) ± SEM after inhalation of salbutamol from the Easyhaler® powder inhaler (MDPI) and from the MDI-spacer combination.

DISCUSSION

When the radiotracer method was evaluated in vitro, activity distribution agreed well with drug content in the respirable parts of the cascade impactor (particle size < 5.8 µm) (Table II). Hence, the amount of radioactivity detected in the lungs and in the oropharynx of the patients reflected the amounts of radiolabelled drug delivered to these sites. Differences between the respirable fraction might lead to overestimation of pulmonary deposition of inhaled salbutamol particles. The difference is, however, in the same range as reported in a previous deposition study (12). Because of the labelling procedure the study was not randomized. All the patients inhaled the radiolabelled inhalation powder on the first day. This minimized the number of radiolabelled batches.

Apparently 10% of the drug dose is retained in the aerosol actuator, whereas larger and more variable fractions of drug doses are retained in powder inhalers. A larger retainment in the powder inhalers is usually due to a more complicated device structure and a larger adhesion plastic wall area. The emptying of the drug dose from the device also depends on the inspiratory flow rate. Thus it can be difficult for obstructive patients to create sufficient air flow rates to deliver the dose effectively. A very low retainment of the dose in the Easyhaler® powder inhaler, 5.6 ± 2.1%, indicated that the device was easily emptied. This is further emphasized by the low retainment of the dose in the inhalers of the most obstructive patients: baseline FEV_1 of 31, 47 and

Table III. Areas under the FEV_1 curves (AUC), maximum FEV_1 values, maximum FEV_1 as a percent predicted of FEV_1 and conventional 90% confidence intervals (CI**) for the ratio MDPI/MDI of the AUC, maximum FEV_1 and maximum FEV_1 of predicted (means).

	Easyhaler®	MDI + spacer	90% CI** Lower	90% CI** Upper
AUC of FEV_1 (l × h)	174	174	0.97	1.03
Maximum FEV_1 (l)	3.0	3.0	0.97	1.03
Maximum FEV_1 of predicted (%)	89	88	0.98	1.03

51% of the predicted value and the retainment of the dose of 4.2, 4.3, and 6.9% of the total drug amount, respectively.

In the powder delivery the upper airway deposition ranged from 62 to 79% of the total dose being on average 71 ± 6%. According to the classic aerosol theory high inspiratory flow rates increase upper airway deposition, because they enhance inertial impaction. In the powder therapy, however, strong inspiration disperses the drug particles most effectively to their primary particles, which reduces the mean particle size distribution and increases pulmonary deposition. The consequence of that is reduced upper airway deposition.

In the powder delivery the mean pulmonary deposition was 24 ± 6% (range 15–33%). The small standard deviation indicated that the construction of Easyhaler® controlled the inspiratory flow rate over a wide range of inspiratory efforts: the values of the PIF ranged from 32 to 65 l/min. There was no correlation between the pulmonary deposition and the inspiratory parameters, but a trend towards higher pulmonary deposition during higher values of PIF could be noticed. In this study high deposition was achieved even at the lowest peak inspiratory flow rates. Thus also the most obstructive patients were able to create sufficient air flow rates to obtain good pulmonary deposition.

Spacer devices are most often used in the delivery of corticosteroids in order to reduce oropharyngeal impaction of the drug. They can, however, also be utilized in the delivery of sympathomimetic drugs especially if patients have problems in drug delivery because of airway obstruction. These devices usually increase pulmonary deposition and clinical response by allowing the velocity of the delivered aerosol spray to slow down and by increasing the respirable fraction of the delivered dose through evaporation of propellants. Thus in this study the most effective means of administering the reference drug was used. Yet the bronchodilating effect was similar to that of the powder delivery. Therefore, inspiratory air flows created by asthmatics were sufficient to disperse the powder formulation and to deliver the drug particles to the site of action in the lower respiratory tract as effectively as the MDI spacer combination did. Both the construction of the powder inhaler and the formulation of the power mixture were suitable for pulmonary drug delivery.

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