

# Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution

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## Abstract

**The lung dose and deposition patterns of drug delivered by dry powder inhaler are not known. The effects of inhaling 400 µg salbutamol delivered by dry powder inhaler (two 200 µg salbutamol Rotacaps), by pressurised metered dose inhaler, and by Acorn nebuliser were studied in nine subjects with chronic stable asthma. Technetium-99m labelled Teflon particles were mixed with micronised salbutamol in the pressurised metered dose inhaler and in the capsules; technetium-99m labelled human serum albumin was mixed with the salbutamol solution for the nebuliser study. The pressurised metered dose inhaler deposited 11.2% (SEM 0.8%) of the dose within the lungs; this was significantly more than the dose deposited by the dry powder inhaler (9.1% (0.6%)), but did not differ significantly from the dose delivered by the nebuliser (9.9% (0.7%)). Distribution within the peripheral third of the lung was significantly greater with the nebuliser than with the other two systems; FEV<sub>1</sub> improved to a significantly greater extent after inhalation of 400 µg salbutamol from the pressurised metered dose inhaler (35.6% from baseline) than from the nebuliser (25.8%) or dry powder inhaler (25.2%). Thus after inhalation of similar doses of salbutamol a larger proportion of drug was deposited within the lungs when it was inhaled from a metered dose inhaler than from a dry powder system; the nebuliser achieved the greatest peripheral deposition. The bronchodilator response seems to depend on the amount of drug within the lungs rather than its pattern of distribution.**

Poor inhaler technique is a common problem among asthmatic patients using pressurised aerosol inhalers.<sup>1-4</sup> Most of them can use a dry powder bronchodilator aerosol more effectively.<sup>4</sup> For children a dry powder inhaler may also be more effective than a pressurised delivery system.<sup>5</sup> Although dry powder inhalers have been used for the management of asthma for more than a decade, very little is known about the pattern of drug delivery

within the body or the amount that is deposited in the lungs.

In an assessment in vitro salbutamol delivery from a dry powder inhaler (Rotacap) appeared to be half as efficient as delivery from the pressurised metered dose inhaler<sup>6</sup>; as a result the dose recommended for patients is twice that of the dose used with the pressurised inhaler. Clinical studies, however, have provided less clearcut conclusions, some showing equipotency for the two forms of delivery<sup>6,7</sup> and others suggesting a better response with the pressurised inhaler system.<sup>8,9</sup> Because of these controversies and the lack of data on deposition patterns of dry powder medication within the respiratory tract, we have compared the deposition pattern of salbutamol administered by dry powder inhaler, from a pressurised metered dose inhaler, and an Acorn nebuliser.

## Methods

### SUBJECTS

We studied nine subjects with chronic stable asthma (three men, six women) aged 20-68 years. They had a history of well documented asthma of 10-60 years' duration and showed an improvement in FEV<sub>1</sub> of more than 15% from baseline after 200 µg of salbutamol delivered by pressurised metered dose inhaler. Their mean baseline FEV<sub>1</sub> was 55% (SD 20%) of the predicted values according to age, sex, and height.<sup>10</sup> All were regularly inhaling corticosteroids and bronchodilators, and three were also taking oral theophylline preparations. Their inhaler techniques were assessed before the study and were found to be satisfactory. They were studied on three occasions at least three days apart to ensure complete decay of the radioactivity. Oral bronchodilators were discontinued 18 hours and inhaled bronchodilators 12 hours before the study but inhaled corticosteroids were continued as usual.

The study was approved by the ethical committee of University College and Middlesex School of Medicine.

### STUDY DESIGN

The aim of the study was to compare the deposition patterns and change in lung function after similar doses of salbutamol given from a pressurised cannister, a dry powder

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inhaler, and an Acorn nebuliser.

The subjects inhaled in random order the following doses of salbutamol mixed with the radionuclide technetium-99m:

- 1 400  $\mu\text{g}$  salbutamol (Ventolin) delivered from a pressurised metered dose inhaler (four puffs, 100  $\mu\text{g}$  a puff), the actuation being made at the beginning of a slow, deep inhalation followed by a 10 second breath hold;
- 2 400  $\mu\text{g}$  salbutamol delivered as a dry powder (two 200  $\mu\text{g}$  salbutamol (Ventolin) Rotacaps) via a Rotahaler, each capsule being inhaled twice rapidly, with a 10 second breath hold on each occasion;
- 3 400  $\mu\text{g}$  salbutamol, nebulised with an Acorn jet nebuliser for the nebuliser study, inhaled through a mouthpiece at tidal volume until the nebuliser was dry.

For each subject the deposition pattern was assessed by gamma camera imaging of the lungs, throat, and abdomen; lung function was assessed by measuring peak expiratory flow (PEF), FEV<sub>1</sub>, and forced vital capacity (FVC). Readings were made -30, -15, 0, 30, 45, and 60 minutes from the time of inhalation and the best of three readings recorded on each occasion.

#### RADIONUCLIDE LABELLING TECHNIQUE

For the pressurised metered dose and dry powder inhalers technetium-99m labelled Teflon (fluorinated ethylene propylene) particles were manufactured by a May spinning disc generator<sup>11,12</sup> and mixed with micronised salbutamol particles in a reconstituted pressurised metered dose inhaler or in capsules as follows. Firstly, <sup>99m</sup>Tc pertechnetate in 10 ml normal saline was passed through a cation exchange column (Amberlite 20) and the eluate collected in a glass container, subsequently evaporated by heating and blowing air across it simultaneously. Next, 0.5 ml of submicron Teflon suspension in 50 ml of 40% ethanol was added to the technetium residue and the solution was run on to the spinning disc revolving at 62 000 rev/min. A 240 watt light bulb served as a heat source within the generator tank to enhance evaporation of liquid droplets and to prevent particle agglomeration.<sup>13</sup> The particles generated were collected by scraping the glass collection plates placed on the base of the tank and transferring the powder into an empty cannister. This was subsequently heated to 240°C to improve the durability of the particles. For the metered dose inhaler preparation 10 GBq of <sup>99m</sup>Tc pertechnetate was initially used to label the Teflon particles with 200–400 MBq radioactivity. An activity of 2 GBq was used in the preparation of the dry powder capsules.

For the reconstitution of the pressurised metered dose inhaler the cannister containing the technetium labelled particles was cooled to -60°C by immersion in solid carbon dioxide. A commercial 80 dose cannister containing micronised salbutamol, chlorofluorocarbon propellants, and surfactant was also cooled down to well below the boiling point of the propellant mixture. The top of the commer-

cial cannister was then quickly removed by a special blade and the contents were transferred into the cannister containing the Teflon particles. A new metering valve was quickly secured in position and crimped to the cannister. The process of transferring the contents and securing the valve was completed in less than 10 seconds to prevent the evaporation of the propellants. The reconstituted cannister was then shaken in an ultrasonic bath for 10 minutes to disperse the particles uniformly. Each actuation released 100  $\mu\text{g}$  salbutamol with 2.0–4.0 MBq of radioactivity.

For the reconstitution of dry powder capsules the <sup>99m</sup>Tc labelled Teflon particles were weighed accurately with an electronic microbalance (Sartorius 1201 MP2) and mixed with premixed micronised salbutamol sulphate in lactose powder of a known weight (in the proportion of 200  $\mu\text{g}$  salbutamol in every 25 mg of powder mixture). The powder mixture was ground thoroughly with a pestle and mortar and passed through a metal sieve several times. The correct proportion of powder mixture was subsequently weighed and transferred into gelatin capsules. Four or five capsules were usually prepared on each occasion; each contained 200  $\mu\text{g}$  salbutamol, 24.8 mg lactose and about 1 mg of technetium-99m labelled Teflon particles with 8–10 MBq of radioactivity. The capsules were then ready for clinical use or performance assessment (quality assurance).

For the nebulised aerosol study 400  $\mu\text{g}$  salbutamol solution (Ventolin) was mixed with 100 MBq <sup>99m</sup>Tc human serum albumin and normal saline was added to make this up to 4 ml. The solution was nebulised to dryness by an Acorn jet nebuliser at 8 litres a minute. The particles produced were inhaled by tidal breathing at a controlled respiratory rate of 18–20 breaths a minute for four minutes. The rate was guided by a metronome and the inspiratory volume by needle deflection on a flow integrator (Gould-Godart).

#### PARTICLE SIZE ANALYSIS

Aluminium foil placed on the base of the generator tank was used to collect the Teflon particles settling from the spinning disc for size analysis with a scanning electron microscope. The particles collected by scraping the glass collection plates were examined in the same way. The size of salbutamol particles from the pressurised metered dose inhaler and nebuliser were analysed separately with a Malvern laser diffractometer.

#### PERFORMANCE ASSESSMENT OF THE RECONSTITUTED METERED DOSE INHALER AND DRY POWDER CAPSULES

The contents of the reconstituted metered dose inhaler cannister were examined by discharging 10 puffs into a Twin Impinger (Glaxo Limited). The Twin Impinger was operated at an air flow of 60 l/min so that the two chamber instrument had a 50% effective cut off diameter of 6.4  $\mu\text{m}$ , particles of this aerodynamic size having a 50% probability of

penetrating to the lower chamber and particles of smaller size having a higher probability of penetration. Methanol was used in both stages as the solvent for collection of salbutamol and Teflon particles. Particles deposited on the actuator and valve and in stages 1 and 2 were assessed for radioactivity with a gamma camera and by assaying for salbutamol spectrophotometrically after the radioactivity had completely decayed.

The reconstituted dry powder capsule containing a mixture of  $^{99m}\text{Tc}$  labelled Teflon and salbutamol sulphate particles in lactose was also assessed with the Twin Impinger. Distilled water was used as the solvent for collection of salbutamol and Teflon particles. After the capsule had been broken into two halves the powder was sucked through the Twin Impinger with an air flow of 60 l/min for five seconds. Both the radioactivity and the drug assay of the contents of the Rotahaler, the remaining capsule, and the powder in stages 1 and 2 were assessed by the techniques used for the pressurised metered dose inhaler.

#### RADIONUCLIDE IMAGING TECHNIQUE

Immediately after inhaling the radiolabelled aerosol subjects had the imaging performed, seated in front of a dual headed gamma camera (Siemens Rota Camera), which can acquire simultaneous anterior and posterior images. Images of the lungs with or without views of the throat or stomach were collected for a count limit of 300 K and those including the throat or stomach were collected for a time limit of 120 seconds. The camera was interfaced to an ADAC computer and the data were stored on magnetic tape for subsequent analysis. Radioactivity retained in tubing, nebuliser, actuator valve, Rotahaler, and capsule were all assessed for a time limit of 100 seconds. Counts in the regions of interest delineating the lungs, throat, and stomach were obtained and expressed as percentages of the initial activity in the nebuliser or capsules and, for the pressurised metered dose inhaler, as percentages of the total activity released. These values were corrected for background activity, attenuation of photons (in the throat, chest, or abdominal walls) and radioactive decay. The lungs were divided into a peripheral third and central two thirds.

Baseline lung function values and percentage total and peripheral lung deposition of radioaerosol with improvement in lung function values (mean (SEM))

	Metered dose inhaler	Dry powder inhaler	Nebuliser
Baseline PEF (l/min)	246 (25)	248 (27)	246 (28)
FEV <sub>1</sub> (l)	1.40 (0.13)	1.42 (0.13)	1.43 (0.15)
FVC (l)	2.25 (0.19)	2.28 (0.18)	2.19 (0.18)
Radioaerosol deposition			
Total lung (%)	11.2 (0.8)	9.1 (0.6)	9.9 (0.7)
Peripheral lung (% of total)	16.1 (1.2)	12.7 (1.3)	24.5 (1.0)
Improvement (%)			
PEF	40.1 (6.6)	32.4 (6.7)	29.9 (5.2)
FEV <sub>1</sub>	35.6 (7.4)	25.2 (6.2)	25.8 (6.5)
FVC	25.4 (4.4)	19.7 (5.3)	24.4 (6.0)

PEF—peak expiratory flow; FEV<sub>1</sub>—forced expiratory volume in one second; FVC—forced vital capacity.

#### STATISTICAL ANALYSIS

Analysis of variance was used to identify differences in baseline values of lung function, total and peripheral deposition of aerosol, and changes in lung function in the three treatment groups. Multiple comparisons between groups were performed by means of a linear contrast method. A *p* value of <0.05 was taken as significant. For the analysis of change in PEF, FEV<sub>1</sub>, and FVC changes at 30, 45, and 60 minutes were added together and the mean values used for the comparison.

#### Results

##### VALIDATION

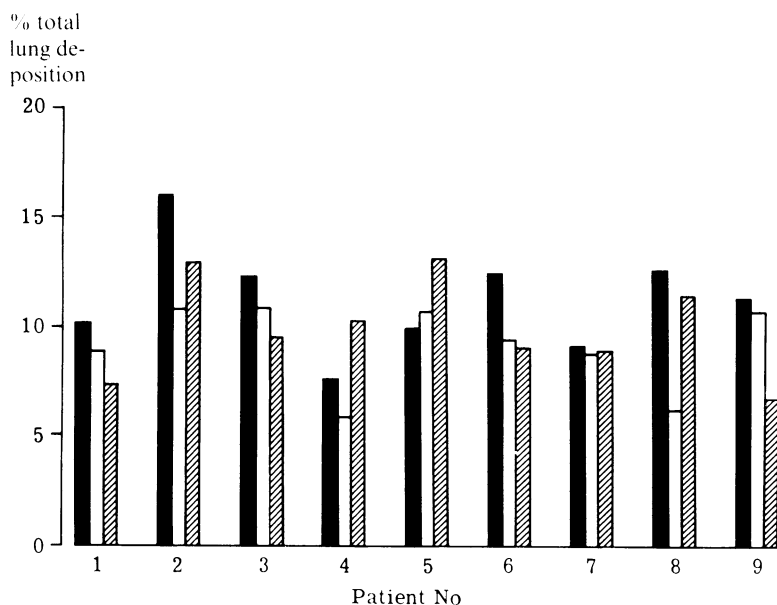
The mass median diameter (MMD) of Teflon particles was 2.1 (SD 1.5)  $\mu\text{m}$  and that of salbutamol was 1.45 (1.4)  $\mu\text{m}$ . The mass median diameter of nebulised  $^{99m}\text{Tc}$  human serum and salbutamol particles was 2.3 (2.4)  $\mu\text{m}$ .

The results of the Twin Impinger study with the pressurised metered dose inhaler showed a mean (SD) percentage radioactivity of 10.2 (3.0), 52.6 (6.0), and 37.1 (6.8) in the actuator, stage 1, and stage 2. The corresponding mean (SD) percentages of salbutamol were 9.7 (2.5), 45.0 (4.3), and 44.7 (4.7). The differences between the radioactivity and the drug were small and considered acceptable. For the dry powder the mean (SD) percentage radioactivity values were 29.5 (4.2), 59.0 (2.1), and 11.5 (3.4) in the Rotahaler, stage 1, and stage 2, compared with 23.5 (2.1), 62.0 (1.4), and 14.5 (0.7) for the drug. In total, 13 runs were performed with a metered dose inhaler and four with a dry powder inhaler.

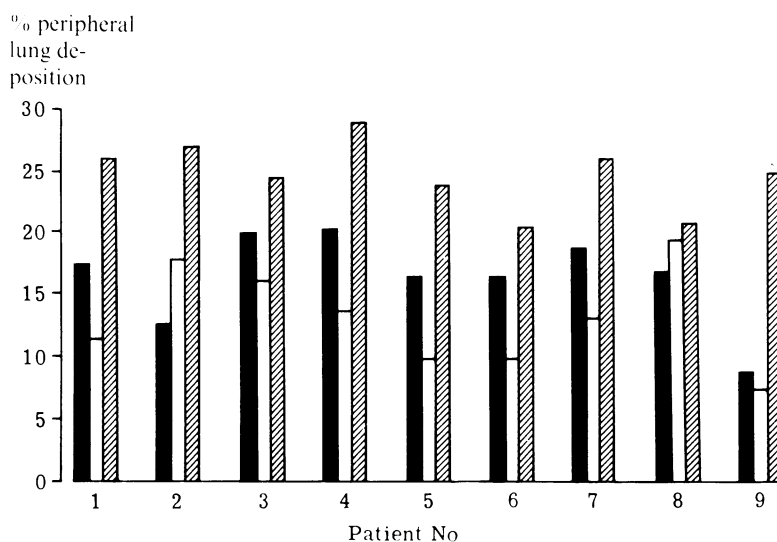
##### IN VIVO STUDY

Mean baseline values of PEF, FEV<sub>1</sub>, and FVC for the three studies were similar (table). The percentage of total deposition and the percentage of the total that entered the peripheral third of the lung in each subject are shown in figure 1. The greatest total lung deposition was achieved after inhalation from the pressurised metered dose inhaler, with a mean (SEM) of 11.2% (0.8%) of the released dose (table). This was significantly greater than the deposition achieved with the dry powder (9.1% (0.6%), *p* < 0.025), but not the acorn nebuliser (9.9% (0.7%)). The mean percentage peripheral lung deposition of aerosol was significantly greater with the nebuliser than the pressurised metered dose inhaler (*p* < 0.001), and the metered dose inhaler was in turn significantly better than the dry powder (*p* < 0.05). The improvement in FEV<sub>1</sub> was significantly greater with the pressurised metered dose inhaler than either the dry powder or the nebuliser (*p* < 0.025). There was no significant difference in FEV<sub>1</sub> between the dry powder and the nebuliser.

The improvement in PEF showed a trend towards a greater response with the metered dose inhaler similar to that of FEV<sub>1</sub>, but the differences between the three methods did not reach statistical significance. The increase in FVC was similar after the three forms of aerosol inhalation.



(a)



(b)

Figure 1 Percentage deposition of radioaerosol in each study in (a) the total lung and (b) the peripheral third of the lung. ■ Metered dose inhaler; □ DPI—dry powder inhaler; ▨ nebuliser.

Figure 2 shows the mean percentage deposition of aerosol at various sites. Gastrointestinal tract deposition was very much greater after administration by pressurised metered dose inhaler and dry powder than with the nebuliser; the amount of drug wasted in the apparatus was largest with the nebuliser. After dry powder inhalation 11.6% of the radioactivity was not accounted for; this was thought to be lost to the air when the capsules were broken before inhalation.

### Discussion

Our study suggests that the salbutamol dry powder inhaler deposits in the lungs about 80% of the dose deposited with the pressurised metered dose inhaler. These findings are supported by the changes in lung function measurements, which agree with the data of Duncan *et al*<sup>6</sup> and Hartley *et al*,<sup>9</sup> who showed a tendency towards a better response with a

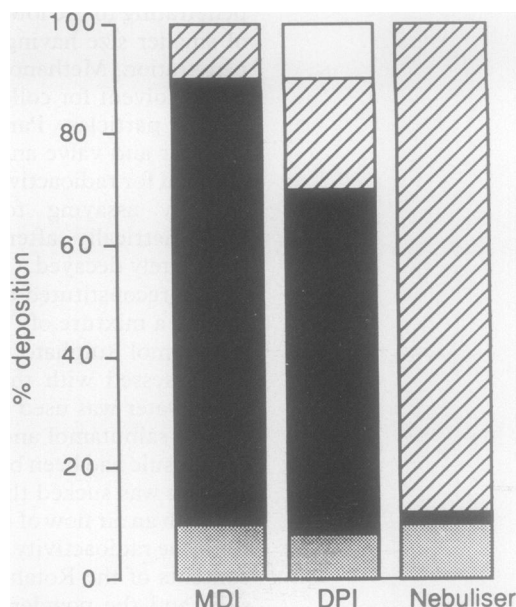


Figure 2 Percentage deposition of aerosol delivered by the metered dose inhaler (MDI), the dry powder inhaler (DPI), and the nebuliser at different sites. ■ Lung; ▨ gastrointestinal tract; ▨ apparatus; ■ loss to the air.

pressurised metered dose inhaler. The use of Teflon particles that are not totally matched to the size distribution of the drug particles may not be ideal, but the differences in size were small and unlikely to have caused important differences in the pattern of deposition. This is certainly true for the pressurised metered dose inhaler, as shown previously.<sup>14</sup> Direct labelling of salbutamol would be ideal for these studies but the technique is not available. Our Twin Impinger data, however, suggest very similar deposition of the drug and Teflon particles. Our results with the pressurised metered dose inhaler are close to previous estimates of doses deposited in the lung.<sup>15-18</sup>

Bronchodilator responses seem to be related more to the total dose of bronchodilator deposited within the lungs than to the pattern of distribution. The response was greatest with the pressurised metered dose inhaler than either the dry powder or the Acorn nebuliser, despite the fact that the nebuliser deposited more drug in the peripheral third of the lung than the other two techniques. Although the total lung dose achieved by the pressurised metered dose inhaler and nebuliser did not differ significantly, the bronchodilator response was greater with the former; this perhaps suggests some contribution from the drug deposited in the oropharynx to bronchodilatation, as noted in previous studies.<sup>19,20</sup>

We have compared the deposition patterns and bronchodilator responses of three commonly used delivery systems for salbutamol. After starting with an identical drug dose the pressurised metered dose inhaler deposits a significantly greater dose within the lungs than the dry powder system and achieves a significantly greater increase in lung function. Nevertheless earlier estimates suggesting that the latter delivers only half as efficiently as the

metered dose inhaler considerably underestimate the dry powder system.

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