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Short Communications

The effect of changes in particle size on the deposition of pressurized inhalation aerosols

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Most patients with reversible airway obstruction use pressurized metered-dose bronchodilator aerosols to control their symptoms, although these devices are very inefficient in their delivery of drugs to the bronchial tree. Only about 10% of the available dose actually reaches the lungs directly (Davies, 1975), but this small percentage of the dose is chiefly responsible for the therapeutic effect (Ruffin et al., 1978). A variety of factors may improve the deposition of pressurized aerosols in the lungs, notably a slow inhaled flow rate (Dolovich et al., 1981; Newman et al., 1981a), breath-holding (Newman et al., 1982a), placing the actuator a few centimetres from the open mouth (Dolovich et al., 1981), the use of extension tubes placed on the actuator mouthpiece (Newman et al., 1981b) and changes in propellant vapour pressure and metered-volume (Newman et al., 1982b). Particle size is probably the most critical factor determining the deposition of stable particles inhaled under steady breathing conditions (Heyder et al., 1980). In this short paper, we report the results of deposition studies in which particles of two different sizes (mass median aerodynamic diameters 3.2 μm and 6.4 μm) have been placed in pressurized canisters and subsequently inhaled by a group of patients with obstructive airway disease.

Pressurized aerosol deposition was measured using particles of Teflon, labelled with the gamma-emitting isotope, $^{99}Tc^{m}$. This technique has already been reported fully elsewhere (Newman et al., 1981b and c). The Teflon particles were manufactured by a spinning disc generator (Camner et al., 1971), situated within an airtight tank. The disc was driven by a compressed air supply, and the particle size was altered by changing the speed of disc rotation (particle size is inversely proportional to disc speed). Particles of two different sizes were made, having mean diameters of

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2 μm (S.D. ± 0.4 μm) and 4 μm (S.D. ± 0.8 μm). Since Teflon has a density of 2.13 $gm \cdot cm^{-3}$, the aerodynamic particle diameters were greater than their geometric diameters by a factor of $\sqrt{2.13}$. The size distributions could therefore be characterized by mass median aerodynamic diameters (MMADs) of 3.2 μm (geometric standard deviation, GSD, 1.2) and 6.4 μm (GSD 1.2). Particle size was checked by allowing particles to settle onto microscope slides on the base of the spinning disc generator tank. The radiolabelled particles were suspended in a mixture of chlorofluorocarbon propellants 11, 12 and 114 (ratio 1 : 2 : 1) together with sorbitan trioleate surfactant (14 $mg \cdot ml^{-1}$) in small aluminium canisters equipped with metering valves. The propellant vapour pressure was 374 kPa at 20 °C and each metered dose released 25 μl of propellants containing the labelled particles. The aerosol was inhaled from the canisters in a controlled manner. The canister was actuated during the early stages (approx. 20% vital capacity) of a deep and slow inhalation (approx. 30 $l \cdot min^{-1}$). Inhalation was followed by a period of 10 s breath-holding.

Distribution of the radiolabelled particles in the oropharynx and lungs, and of swallowed particles located in the stomach, was assessed from profile scans of the head and trunk using a whole body counter (Newman et al. 1981b and c). Extrathoracic deposition was calculated as the sum of particles initially deposited in the oropharynx and particles located on the actuator. The percentage of the dose located on an expired air filter was also measured. Whole lung deposition and extrathoracic deposition were expressed as percentages of the administered dose. Aerosol located in the lungs was fractionated into that initially deposited on the conducting airways (tracheobronchial zone) and that initially deposited in the alveoli, on the assumption that particles measured in the lungs after 24 h constituted alveolar deposition (Camner and Philipson, 1978).

Deposition was measured in 10 ambulant out-patients with obstructive airway disease (6 asthmatics, 4 bronchitics, mean age 57 ± 15 (mean ± S.D.) years, mean forced expiratory volume in one second (FEV_1) 66 ± 27% predicted). Six patients were male and four female. Each patient performed 2 studies on 2 separate occasions in a randomised order, inhaling either 3.2 μm or 6.4 μm MMAD particles. Pressurized aerosol deposition patterns for the 2 particle sizes are shown in Fig. 1. There was no significant difference in whole lung deposition between 3.2 μm and 6.4 μm MMAD particles (11.4 ± 2.0% (mean ± S.E.M.) and 11.5 ± 1.4% of the dose, respectively). Alveolar and tracheobronchial depositions were also similar for the two particle sizes. Extrathoracic deposition was virtually unchanged by the increase in particle size (88.0 ± 2.3% of the dose for the 3.2 μm particles and 87.7 ± 1.4% of the dose for the 6.4 μm particles). Only about 1% of the dose was exhaled for each particle size. Inhaled volumes (2.07 ± 0.26 litres and 1.91 ± 0.23 litres) and average inhaled flow rates (29.1 ± 4.6 $l \cdot min^{-1}$ and 29.9 ± 4.6 $l \cdot min^{-1}$) were very similar for the two study days.

It is concluded that a change in particle size of a metered-dose aerosol from MMAD 3.2 μm to 6.4 μm alters neither the amount of aerosol able to reach the lungs nor the distribution pattern within the bronchial tree. By contrast, a rise in particle size markedly affects the deposition of stable dust particles inhaled during steady breathing in that deposition in the oropharynx is enhanced, whole lung

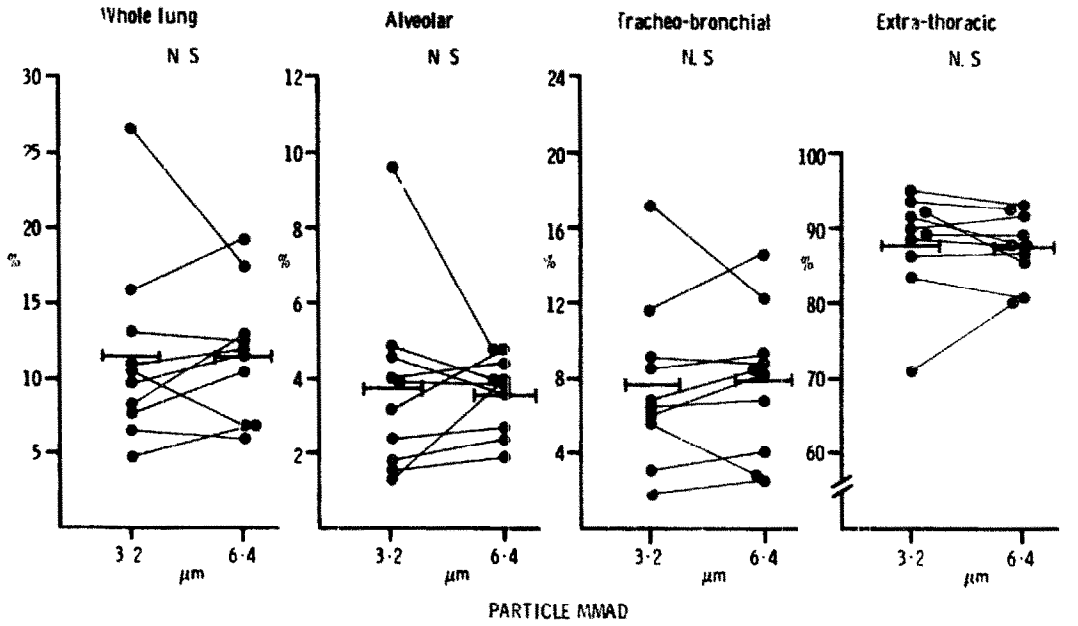

Fig. 1. Whole lung, alveolar, tracheobronchial and extrathoracic deposition for particles of MMADs 3.2 μm and 6.4 μm in 10 patients with obstructive airway disease.

deposition is reduced and the distribution of aerosol particles within the lungs is less peripheral (Heyder et al., 1980). These features of aerosol deposition were not observed in the present study, suggesting fundamental differences between stable dust particles and pressurized aerosols, probably related to the presence of unevaporated chlorofluorocarbon propellants in the latter. It is commonly believed that the propellants evaporate as soon as the spray leaves the canister, but in fact this is not the case. Only the minority of the propellants 'flash' upon actuation, and the majority evaporate at a much slower rate as the aerosol moves away from the canister (Sanders, 1970). Furthermore, the solid particles are coated with non-volatile surfactant. Deposition in this study may have been independent of particle size because of surfactant and unevaporated propellant coating the particles, producing an effective aerosol diameter greater than both sizes of particle employed. Laser holographic studies on terbutaline sulphate metered-dose aerosol have shown that even at a distance of 25 cm from the actuator orifice, the aerosol mass median diameter (MMD) may exceed 10 μm, even though the drug crystals themselves have an MMD of approximately 3 μm (Morén and Andersson, 1980). Because of the large size and rapid velocity (Rance, 1974) of the propellant droplets, most are deposited in the oropharynx, while stable dust particles more readily follow the inhaled airstream.

Changes in both propellant vapour pressure and metered-volume size alter the pattern of pressurized aerosol deposition in the respiratory tract (Newman et al, 1982b) presumably because changes in these formulation factors alter the size of the propellant droplets within which the drug crystals are enclosed (Polli et al., 1969). Changes in metered-dose aerosol formulation thus appear to be more important than

changes in drug crystal size in determining the site of deposition within the respiratory tract, at least for particles within the range 3.2–6.4 μm. Larger drug particles may penetrate less readily into the respiratory tract, however, and may hence be less effective. There have been only limited studies on the bronchodilator efficacy of drug crystals of different sizes, but Rees et al. (1982) found that the bronchodilator response to terbutaline sulphate pressurized aerosol was reduced for particles with MMDs 9.1 μm and 13.6 μm compared to particles of MMD 5.6 μm.

The results of this study support the use of monodisperse radiolabelled Teflon particles as an analogue for polydisperse drug crystals in a pressurized aerosol formulation, since in each case the deposition pattern may depend primarily upon the propellant droplet size rather than upon the size distribution of the suspended particles. Drug particles are hygroscopic and grow in size when they enter the lung. However, the increase in MMAD of metered-dose bronchodilators and corticosteroids is only about 25% (Hiller et al., 1981), and this would be expected to have little effect upon the site of deposition.

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