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# FRACTION OF DOSE EXHALED AFTER ADMINISTRATION OF PRESSURIZED INHALATION AEROSOLS

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## SUMMARY

After the administration of a pressurized inhalation aerosol, a fraction of the dose will be lost with the exhaled air. In the present study suspension aerosols containing a freely water-soluble drug, terbutaline sulphate, and a practically insoluble drug, budesonide, were administered to 10 healthy subjects. The air flow rate, the tidal volume, and the moment of actuation were registered for each of the inhaled doses. The exhalation was performed without any breath-holding pause. The drug in the exhaled air was collected on a membrane filter and in an absorbing solution. The fraction of the dose lost with the exhaled air was less than 1% for both drugs. Differences in air flow rate and tidal volume did not affect the results. A particle growth due to moisture absorption did not appear to be important for the total drug deposition in the respiratory tract.

## INTRODUCTION

Whenever a drug is administered from a pressurized inhalation aerosol, some drug substance is deposited in the respiratory tract during the phases of inhalation, breath-holding, and exhalation. A fraction will not be deposited, but is lost with the exhaled air. The main mechanisms for aerosol deposition are impaction, sedimentation, and diffusion (Gorman and Hall, 1973). Both sedimentation and diffusion are time-dependent, which means that the deposition due to these mechanisms increases the longer the particles are kept in the respiratory tract, for instance by means of a breath-holding pause (Palmes et al., 1973). Particle size is an important parameter for the deposition of an aerosol. The influence of the various deposition mechanisms results in a minimum for particles of about 0.5 μm diameter. Consequently, particles of such size are most readily lost with the exhaled air. The deposition pattern can be modified by a changing particle size during the

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residence time in the respiratory tract. This may occur as a growth of hygroscopic particles (Byron et al., 1977; Davis and Bubb, 1978). An increase in particle size was shown in the aerosol cloud from pressurized aerosols at high relative humidity (Hiller et al., 1980). The particle growth was different for various products: solution aerosols showed a greater increase than suspension aerosols.

In the present study, the fraction of drug substance was determined in the exhaled air from healthy volunteers after the administration of pressurized aerosols containing a freely water-soluble drug, terbutaline sulphate, or a practically insoluble drug, budesonide, both formulated as suspension aerosols. The actuation was performed at the beginning of a deep and slow inhalation according to the normal instructions to patients, but the following exhalation was started directly without any breath-holding pause.

## MATERIALS AND METHODS

A pressurized aerosol was used with a mean valve delivery of 226 μg terbutaline sulphate (Bricanyl, AB Draco, Sweden), or 23.4 μg budesonide (Thalén and Brattsand, 1979), determined after sampling under the surface of chloroform (Morén, 1978). In both formulations the chlorofluorocarbons 11, 12 and 114 were used as propellants and sorbitan trioleate as a surfactant. The mass median diameter was 2.7 μm for the micronized terbutaline sulphate and 3.5 μm for the micronized budesonide (Coulter Counter, Coulter Electronics). The densities of the drugs were 1.28 $g \cdot ml^{-1}$ and 1.24 $g \cdot ml^{-1}$ respectively. The oral actuator was combined with a pear-shaped extension tube (250 mm length; 130 mm maximum inner diameter). This device was earlier shown to reduce the drug deposition in the oral cavity and to increase the availability into the remaining part of the respiratory tract (Morén, 1978). The upper end of the actuator was sealed by means of a rubber film, and all the inhaled air had to pass through the tube of a hot wire spirometer (Model 403, Monaghan) attached to the back of the actuator, see Fig. 1. Furthermore, the actuator was provided with an infrared light-emitting diode and a photo transis-

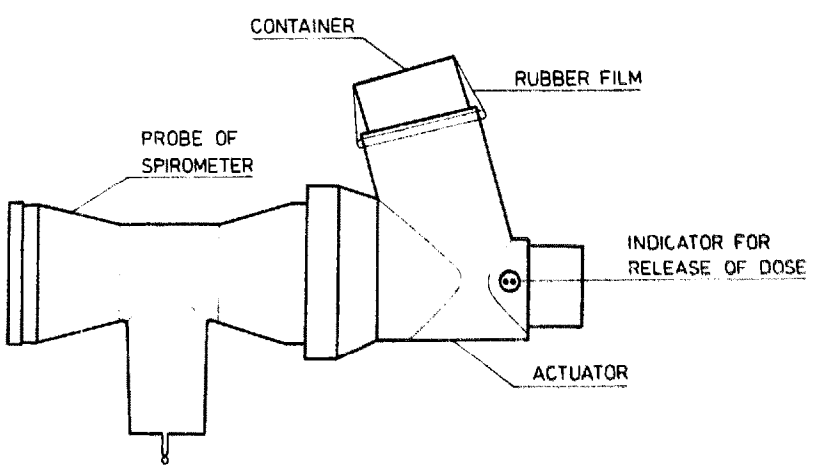


Fig. 1. Modifications of an aerosol actuator for registration of air flow rate, tidal volume and actuation.

tor to detect the release of a dose. An oscilloscope was used to register the air flow rate and the tidal volume (the flow volume curve) for each inhalation and to indicate when the dose was actuated, see Fig. 2. The equipment was calibrated by means of known air volumes. Photographs of the screen were used to read the air flow rate at actuation, the tidal volume, and the actuation relative to the tidal volume.

Ten healthy subjects were trained to actuate the dose at the beginning of a slow and deep inhalation and to start the exhalation without any breath-holding pause. The exhalation was made through a tube provided with a 0.22 $\mu$m membrane filter (MF, Millipore). In the case of budesonide, the filter was extracted with chloroform before the test to avoid interferences in the assay. A washing bottle was connected after the filter to collect the drug substance that could pass through the filter after dissolution in the humid atmosphere. The washing bottle contained 40 ml of an absorbing solution: distilled water for terbutaline sulphate and ethanol for budesonide. The air flow rate at exhalation was adjusted to 30 litres · $min^{-1}$ by means of a vacuum pump.

On each occasion, 8 doses were administered with an interval of at least 1 min between each dose. The inhalation of a dose was followed by two exhalations through the filter. In a separate study, it was found that more than 90% was recovered from the first of two exhalations. The subjects were tested with each of the two drugs in a random order. After each test, the drug substance was determined in the exhalation tube, on the filter, and in the absorbing solution. For the assay of terbutaline sulphate, the exhalation tube and the filter were washed with ethanol–water 50 : 50 (v/v). All the solutions were spectrophotometrically assayed after reaction with 4-aminoantipyrine and potassium ferricyanide at pH 9.5 (Morén, 1978). In the case of budesonide, the exhalation tube and the filter were washed with chloroform. Fluocinolone acetonide was added as an internal standard to

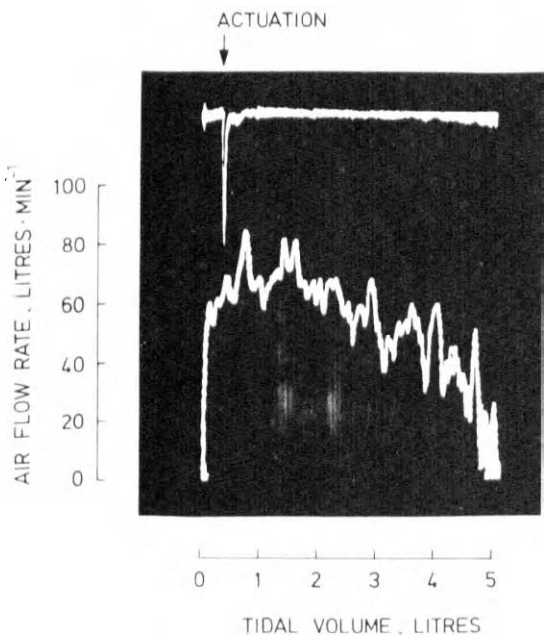


Fig. 2. Flow volume curve and moment of actuation shown on an oscilloscope at inhalation of one dose from a pressurized aerosol.

ditions were used: Model M 6000 solvent delivery system, M 440 UV detector (254 nm) and μ-Bondapak-CN column, Waters Associates; mobile phase heptane–ethanol 80 : 20 (v/v); flow rate 1.0 ml · $min^{-1}$; injection volume 200 μl.

The percentage of exhaled drug was calculated on the basis of the valve delivery for the aerosols. Statistical comparisons between the test series were made by means of paired *t*-tests.

## RESULTS AND DISCUSSIONS

Table 1 shows the conditions for administration of the pressurized aerosols containing terbutaline sulphate and budesonide. The air flow rate at actuation was higher in the budesonide test series; otherwise the conditions were not significantly different. The fractions of exhaled drug were low: 0.7% for terbutaline sulphate and 0.6% for budesonide. No correlation could be demonstrated between the exhaled fraction and the air flow rate at actuation or the tidal volume (Fig. 3). Thus, the difference in air flow rate between the test series probably did not influence the comparison of the exhaled fractions.

A low amount of terbutaline sulphate lost with the exhaled air is in agreement with the results found by Nilsson et al. (1966) for tritium-labelled pressurized aerosols given to 3 subjects. We expected a difference between the drugs tested because of the different water solubilities: 250 mg · $ml^{-1}$ for terbutaline sulphate and 14 μg · $ml^{-1}$ for budesonide. Particles of the former substance will probably grow to a greater extent from moisture absorption in the respiratory tract than particles of the latter substance (Task Group on Lung Dynamics. 1966).

We tried to simulate the moisture absorption of the aerosol particles in the respiratory tract by letting a subject make a pause in an exhalation, actuate a dose from the inhalation aerosol and keep the aerosol cloud in the mouth for different lengths of time (5–30 s). The aerosol cloud was then rapidly exhaled on a glass slide. The deposited particles were immediately examined in a polarization microscope. Crystalline budesonide particles could still be demonstrated after 30 s, but crystalline terbutaline sulphate particles were practically absent after 5 s. Apparently aerosol particles of terbutaline sulphate dissolve and grow much faster in a warm and humid atmosphere. However, a particle growth due to moisture absorption is probably not important for the total drug deposition in the

TABLE 1

ADMINISTRATION OF THE PRESSURIZED INHALATION AEROSOLS

| Drug | Air flow rate at actuation (litres · $min^{-1}$) | Tidal volume (litres) | Fraction of tidal volume at actuation (per cent) | Fraction of exhaled drug (per cent) |
|---|---|---|---|---|
| Terbutaline sulphate | 58 ± 17 | 4.3 ± 1.2 | 8.8 ± 5.6 | 0.7 ± 0.3 |
| Budesonide | 69 ± 14 [a] | 4.4 ± 1.1 N.S. | 8.7 ± 6.3 N.S. | 0.6 ± 0.3 N.S. |

Mean value and S.D. from 10 subjects.
[a] $P < 0.05$; N.S. not significant ($P > 0.05$).

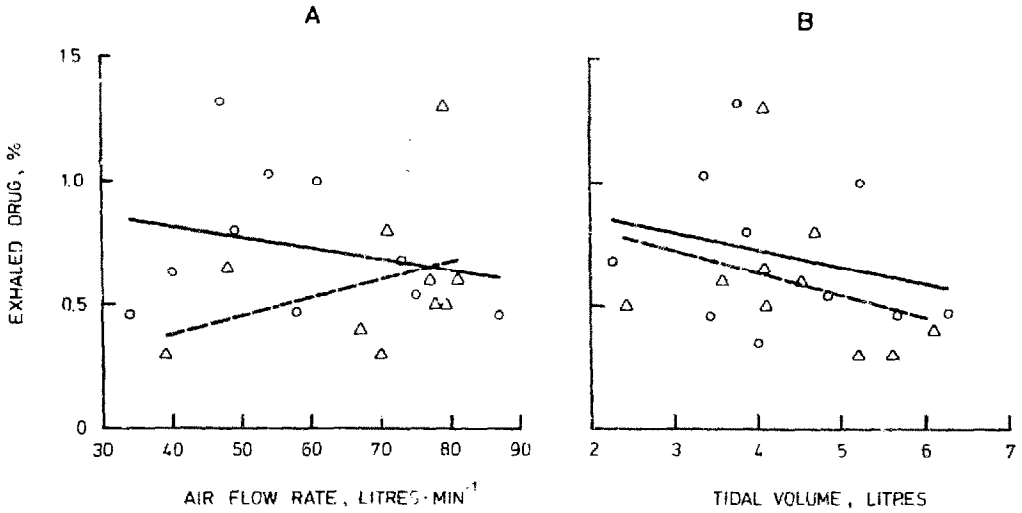


Fig. 3. Fraction of exhaled drug vs various air flow rates at actuation (A) and tidal volumes (B). o———o, terbutaline sulphate; Δ— — —Δ, budesonide.

these solutions and to the absorbing solution. All the solutions were evaporated and the residues were dissolved in 2 ml of the mobile phase used in an HPLC assay. A budesonide standard solution was treated in the same way. The following HPLC equipment and con- respiratory tract, as the exhaled fractions of terbutaline sulphate and budesonide were equivalent.

One reason for the low fractions of exhaled drug is probably a high initial loss due to impaction. In an earlier study, the loss in the device and the mouth was shown to be 31–54% of the delivered dose (Morén, 1978). The impaction is dependent on the size and the velocity of the aerosol particles, and these parameters change after the primary generation of the aerosol cloud. At the actuation, all the propellants will not evaporate immediately (Wiener, 1958). As the various propellants in the formulation have different boiling points, they are likely to have different influences on the aerosol characteristics.

A low-boiling propellant will contribute more to the initial velocity of the aerosol droplets, but it will probably stay for a shorter time in the liquid phase. The size of the generated droplets will decrease over a distance until the evaporation of all the propellants is completed. The non-volatile surfactant will then partly cover the individual drug particles. The presence of liquid propellants and a surfactant will make the droplets larger than the size of the incorporated drug particles. Pilot studies by means of holographic microscopy confirm that the size of the generated aerosol droplets is large at the opening of the actuator. The mass median diameter was 36 μm, decreasing to 12 μm at a distance of 10 cm. At 25 cm, however, any further reduction in size was only marginal.

Apparently, different conditions for the particle size and the particle velocity could be obtained for a pressurized aerosol dependent on such parameters as the propellant mixture, the presence of solutes, and the distance to the subject. In the present study the inhalation was performed by means of an extension tube attached to the actuator. When the actuator is used on its own, a still smaller fraction of the delivered dose can be expected in the exhaled air. No breath-holding pause was used in the study, but it seems

as if the total deposition could only be marginally increased as a result of this manoeuvre. Still, a breath-holding pause may be beneficial for the efficacy on patients, if it increases the drug deposition in the lower respiratory tract.

The modified actuator proved capable of registering the flow volume curve at inhalation and the moment of actuation. The equipment could also be valuable for tests on patients in order to indicate how they manage to follow the instructions for aerosol administration as well as to register whether the conditions are equivalent with regard to the administration of different drugs in comparative clinical trials. In most trials the inhalation technique is not controlled objectively, but it is probable that variations in the technique can influence the efficacy of an inhalation aerosol.

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