International Journal of Pharmaceutics, 11 (1982) 337–344
Elsevier Biomedical Press

The effects of changes in metered volume and propellant vapour pressure on the deposition of pressurized inhalation aerosols

S.P. Newman *, F. Morén **, D. Pavia ***, O. Corrado *** and S.W. Clarke ***

*Departments of * Medical Physics and *** Thoracic Medicine, Royal Free Hospital, London NW3 2QG (U.K.) and ** AB Draco, subsidiary to AB Astra, Box 1707, S-221 01 Lund (Sweden)*

(Received January 22nd, 1982)
(Accepted February 16th, 1982)

Summary

The effects of changes in metered volume and propellant vapour pressure on the deposition of a pressurized inhalation aerosol have been studied in 10 patients with obstructive airway disease. Particles of Teflon (mass median aerodynamic diameter 3.2. μm), labelled with $^{99}Tc^{m}$, were incorporated into canisters formulated with two different metered volume sizes (25 and 50 μl) and with two different propellant vapour pressures (374 and 502 kP_a). Increasing the metered volume had no effect on the quantity of aerosol deposited in the lungs, but produced a significantly ($P < 0.05$) more central pattern of deposition within the bronchial tree. An increase in vapour pressure resulted in a significant ($P < 0.05$) increase in whole lung deposition and a significant ($P < 0.05$) reduction in extrathoracic deposition. It is concluded that changes in formulation alter the deposition pattern of metered dose aerosols, and might consequently bring about changes in clinical efficacy.

Introduction

Bronchodilating agents are widely available in the form of pressurized inhalation aerosols. The active drug is either suspended or dissolved in chlorofluorocarbon propellants at a high pressure in a small canister. It is a common misconception that the propellants evaporate immediately following actuation, leaving small particles of the active drug available for inhalation. In fact, only a small fraction of the propellants 'flashes' immediately, and the remainder is lost at a much slower rate during the passage of the drug particles through air (Sanders, 1970). At the actuator orifice, the propellant droplets may have a mass median diameter exceeding 35 μm

0378-5173/82/0000–0000/$02.75 © 1982 Elsevier Biomedical Press

(Morén and Andersson, 1980), and a velocity greater than 30 $m \cdot s^{-1}$ (Rance, 1974). Large rapidly moving particles are very susceptible to deposition in the oropharynx by the process of inertial impaction and in practice more than 80% of the dose may be deposited in this region and is unable to reach the lungs directly (Newman et al., 1981a).

The propellant droplet size distribution may be changed by several factors, including the metered volume (Morén, 1978) and the propellant vapour pressure (Polli et al., 1969). Furthermore, droplet velocity increases with increasing vapour pressure (Rance, 1974). Aerosol deposition is in turn critically dependent upon particle size and velocity (Lippmann and Albert, 1969). We have therefore tested the effects of changes in metered volume and propellant vapour pressure on the deposition of a pressurized inhalation aerosol, using an in vivo radioaerosol technique.

Materials and methods

Radioaerosol technique

The technique used to measure pressurized aerosol deposition has been described more fully elsewhere (Newman et al., 1981a and b). Briefly, a spinning disc generator (May, 1949) was used to make particles of Teflon (mass median aerodynamic diameter (MMAD) 3.2 μm, geometric standard deviation 1.2), labelled with the radioisotope $^{99}Tc^{m}$. The particles were incorporated together with chlorofluorocarbon propellants into placebo pressurized canisters of the type normally used for the delivery of terbutaline sulphate bronchodilator aerosol (Bricanyl, Astra Pharmaceuticals). We believe that the aerodynamic behaviour of the Teflon particles is similar to that of terbutaline sulphate drug crystals which also have an MMAD of 3.2 μm (Morén and Andersson, 1980).

The aerosol was inhaled under controlled conditions with the actuator connected in series with a heated pneumotachygraph (Newman et al., 1981a). The aerosol was actuated during the early stages (20% vital capacity) of slow (25 $\mu l \cdot min^{-1}$) deep inhalations, followed by a 10-s breath-holding pause. This inhalation mode had been shown previously (Newman et al., 1982) to give maximum deposition of pressurized aerosol in the lungs. Six puffs of aerosol were given in order to obtain adequate radioactive counts.

The subsequent distribution of radioaerosol in head, chest and abdomen was determined from profile scans using a whole body counter with a slit collimator (Tothill and Galt, 1971). The profile scans consisted of 3 peaks corresponding to particles located in 3 characteristic zones—the oropharynx, the lungs and the stomach. Those particles located in the stomach had been initially deposited in the oropharynx and subsequently swallowed. Calculations of the area under each peak, with appropriate corrections for body size, enabled the amount of aerosol located in each zone to be determined. The amounts of aerosol located in mouth-washings, in expired air and on the actuator were also measured. Oropharyngeal deposition was calculated as the sum of radioaerosol measured over the oropharynx (profile scan)

and stomach (profile scan) and recovered in mouth-washings. Extrathoracic deposition was calculated as the sum of oropharyngeal and actuator depositions. Aerosol in the lungs was subsequently divided into conducting airway and alveolar fractions. Alveolar deposition was determined by measuring the 24-h whole lung retention of radioaerosol, assuming that particles deposited on the conducting airways had been removed by the process of mucociliary clearance by that time (Camner and Philipson, 1978). Alveolar deposition expressed relative to whole lung deposition was termed the alveolar deposition fraction.

Aerosol formulations

Three different formulations were tested (Table 1). Aerosol canisters were equipped with metering valves which delivered either 25 or 50 μl of propellant in each metered dose. The propellant vapour pressure was either 374 or 502 kP_a at 20°C. The standard formulation for terbutaline sulphate pressurized aerosol (Bricanyl, Astra Pharmaceuticals) has a metered volume of 25 μl and a vapour pressure of 374 kP_a so that it was possible to assess the effects of increasing the metered volume and the vapour pressure by comparing formulations A and B, and A and C, respectively. Sorbitan trioleate surfactant was included in each formulation at a concentration of 14 $mg \cdot ml^{-1}$. The temperature of the laboratory in which the studies were performed was maintained between 20 and 23°C throughout the experiments.

Patients

Ten patients with obstructive airway disease were studied (5 asthmatics, 5 chronic bronchitics, Table 2). All patients were taking bronchodilator aerosols on a regular basis. Each patient performed 3 tests in a random order (aerosol formulations A, B and C). Simple spirometric tests were carried out immediately before aerosol inhalation in order to assess the degree of airway obstruction. All patients gave informed written consent and the studies were approved by the Hospital Ethical Practices Committee.

TABLE I

DETAILS OF PROPELLANT COMPOSITION, VAPOUR PRESSURE AND METERING VOLUME OF PRESSURIZED AEROSOLS

	Formulation		
	A	B	C
Propellant 11 concentration ($mg \cdot ml^{-1}$)	344	344	207
Propellant 114 concentration ($mg \cdot ml^{-1}$)	344	344	0
Propellant 12 concentration ($mg \cdot ml^{-1}$)	688	688	1174
Vapour pressure (kP_a) at 20°C	374	374	502
Metering volume (μl)	25	50	25

TABLE 2

DETAILS OF PATIENTS STUDIED

Patient no.	Age (years)	Sex	Diagnosis	Smoking history (pack-years) [a]	Forced expiratory volume in 1 s (% predicted)
1	31	F	Asthma	2	102.5
2	67	M	Bronchitis	52	38.5
3	54	F	Asthma	30	47.4
4	69	M	Bronchitis	56	28.9
5	30	F	Asthma	0	69.5
6	75	M	Bronchitis	50	23.8
7	63	F	Asthma	0	75.7
8	57	M	Bronchitis	180	60.4
9	65	F	Bronchitis	62	27.0
10	52	F	Asthma	15	119.0
Mean	56.3			44.7	59.4
S.D.	15.3			53.5	32.8

[a] 20 cigarettes per day for 1 year = 1 pack-year.

Statistical analysis

The data were not assumed to be normally distributed and were analyzed by non-parametric methods using the Wilcoxon rank sum test and the Friedman analysis of variance by ranks (Siegel, 1956).

Results

Metered volume

The mean effect on pressurized aerosol deposition of increasing the metered volume from 25 μl (formulation A) to 50 μl (formulation B) is shown in Table 3. Individual data for whole lung deposition, alveolar deposition fraction and extrathoracic deposition are shown in Fig. 1. Whole lung deposition rose in 4 patients, fell in 5 patients and was unchanged in the remaining patient. However, alveolar deposition was reduced and conducting airway deposition increased, in such a way that the alveolar deposition fraction was significantly ($P < 0.05$) reduced in 9 of 10 patients by increasing the metered volume. This indicated a more central deposition of aerosol within the lungs for the higher metered volume. Oropharyngeal, actuator and extrathoracic depositions, and exhaled aerosol were unchanged by the rise in metered volume.

Vapour pressure

When the propellant vapour pressure was raised from 374 kP_a (formulation A) to 502 kP_a (formulation C) (Table 3 and Fig. 2), whole lung deposition rose significantly ($P < 0.05$) in 9 of 10 patients. Conducting airway and alveolar depositions were both

TABLE 3

MEAN (S.E.M.) PRESSURIZED RADIOAEROSOL DEPOSITION FOR FORMULATIONS A, B AND C

	FORMULATION		
	A	B	C
Conducting airway deposition (% of dose)	9.5 (1.4)	10.4 (1.1)	12.3 (1.2)
Alveolar deposition (% of dose)	4.1 (0.9)	2.8 (0.4)	5.3 (0.9)
Whole lung deposition (% of dose)	13.6 (2.0)	13.2 (1.4)	17.6 (1.9) [a]
Alveolar deposition fraction	0.30 (0.04)	0.21 (0.02) [a]	0.28 (0.03)
% of dose recovered in mouth-washings	37.8 (5.5)	28.8 (5.4)	23.0 (4.0) [b]
% of dose detected over oropharynx	8.5 (1.5)	8.9 (1.5)	10.6 (1.5)
% of dose detected over stomach	29.0 (4.7)	39.4 (5.7)	39.2 (5.7)
Oropharyngeal deposition (% of dose)	75.3 (2.2)	77.1 (1.3)	72.8 (2.1)
Actuator deposition (% of dose)	9.6 (1.5)	8.6 (1.8)	8.3 (1.2)
Extrathoracic deposition (% of dose)	84.9 (1.9)	85.7 (1.5)	81.0 (2.0) [a]
Exhaled aerosol (% of dose)	1.5 (0.6)	1.1 (0.3)	1.4 (0.4)

P values compared with formulation A: [a] $P<0.05$: [b] $P=0.02$.

increased by the rise in vapour pressure, but these rises were not significant. There was little change in alveolar deposition when expressed as a fraction of whole lung deposition. A significant reduction occurred in the amount of aerosol recovered in

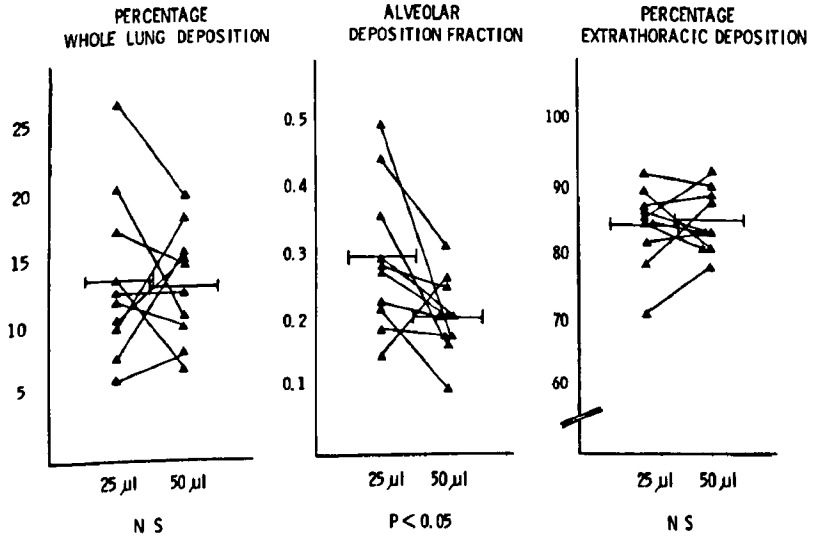

Fig. 1. Effect of metered volume on pressurized aerosol deposition. The changes in whole lung deposition, alveolar deposition fraction and extrathoracic deposition resulting from a rise in metered volume from 25 µl (formulation A) to 50 µl (formulation B) are shown.

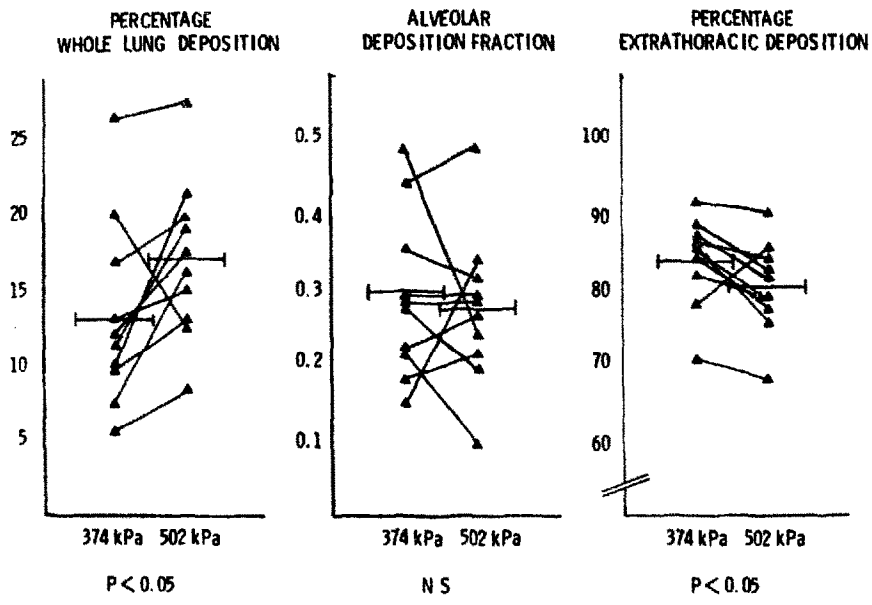

Fig. 2. Effect of propellant vapour pressure on pressurized aerosol deposition. The changes in whole lung deposition, alveolar deposition fraction and extrathoracic deposition resulting from a rise in propellant vapour pressure from 374 kP_a (formulation A) to 502 kP_a (formulation C) are shown. Vapour pressures are at 20°C.

mouth-washings ($P = 0.02$), although oropharyngeal deposition was not significantly altered. Extrathoracic deposition was significantly ($P < 0.05$) decreased in 9 of 10 patients for formulation C. There was little alteration in the amount of aerosol exhaled.

Lung function and inhalation parameters

Within the 3 study days, forced expiratory volume in 1 second (FEV_1) and forced expiratory flow rate at 25% vital capacity ($\dot{V}_{max}$ 25), measured immediately before aerosol inhalation, were similar (Table 4). There were no significant differences in the volume of inhalation (V_I), average inhaled flow rate ($\dot{V}_{av}$) and in the inhaled flow rate at the instant of aerosol actuation ($\dot{V}_{inst}$) for the 3 studies (Table 4).

TABLE 4

MEAN (S.E.M.) LUNG FUNCTION DETAILS AND PARAMETERS OF AEROSOL INHALATION

	FORMULATION		
	A	B	C
FEV_1 (l)	1.46 (0.23)	1.37 (0.24)	1.42 (0.26)
$\dot{V}_{max}$ 25 ($l \cdot s^{-1}$)	0.47 (0.12)	0.34 (0.10)	0.43 (0.13)
V_I (l)	2.18 (0.22)	2.01 (0.22)	2.12 (0.22)
$\dot{V}_{av}$ ($l \cdot min^{-1}$)	25.3 (2.5)	24.1 (1.7)	26.0 (2.2)
$\dot{V}_{inst}$ ($l \cdot min^{-1}$)	32.6 (3.4)	31.5 (2.6)	33.9 (2.6)

Discussion

These results confirm the findings of earlier studies (Newman et al., 1981a and b) that the majority of the dose from a pressurized inhalation aerosol is deposited in the oropharynx and that only a small amount reaches the lungs. Pressurized aerosol deposition may be altered by changes in the inhaled flow rate, breath-holding pause and the lung volume of actuation (Newman et al., 1982) but these factors were kept constant in the present study. The pattern of radioaerosol deposition for formulation A was similar to that obtained previously for the same inhalation mode (Newman et al., 1982).

The amount of aerosol deposited in the lungs was unchanged by doubling the quantity of propellant released in each metered dose, but alveolar deposition expressed relative to whole lung deposition was significantly reduced. This indicated a more central deposition pattern within the lungs. It is likely that the release of a higher propellant volume per actuation retards the evaporation of the propellant droplets, since evaporation depends upon the acquisition of heat from the surrounding atmosphere as the particles pass through air (Sanders, 1970). Aerosol particles are less able to penetrate to the lung periphery as their size increases (Pavia and Thomson, 1976). In an earlier study (Morén, 1978) the amounts of a bronchodilator drug lost on the actuator, in mouth-washings and in a 10 cm extension tube were measured for metered volumes of 25, 50 and 100 μl. Overall, there was a significant increase in drug losses with increasing metered volume, but there was little difference between the results with 25 μl and with 50 μl, in agreement with the present study.

An increase in propellant vapour pressure has two effects on the propellant droplets. There is a higher initial droplet velocity (Rance, 1974), but smaller initial droplets and more rapid evaporation (Wiener, 1958; Polli et al., 1969). Inertial impaction of aerosol droplets in extrathoracic regions is increased by raising their velocity but is decreased by reducing their size (Lippmann and Albert, 1969). In the present study, the latter effect was apparently dominant, since extrathoracic deposition was reduced and whole lung deposition increased by the rise in vapour pressure. These results were in broad agreement with a previous study (Morén, 1978) in which the same increase in vapour pressure brought about a reduction of drug losses in mouth-washings and in an extension tube.

Changes in bronchodilator aerosol deposition in the lungs may bring about important alterations in clinical efficacy since the therapeutic effect is thought to depend upon the small fraction of the aerosol dose that actually gets into the lungs (Ruffin et al., 1978). Previous studies from our laboratory suggest that the bronchodilator response may be directly related to the quantity of aerosol landing on the airways. Changes in the inhaled flow rate and the subsequent duration of breath-holding bring about significant rises in both whole lung deposition of pressurized aerosol (Newman et al., 1982) and bronchodilator response to an inhaled β-agonist (Newman et al., 1981c). The use of extension divices placed on the aerosol actuator also enhances both whole lung deposition (Newman et al., 1981b) and clinical efficacy (Ellul-Micaleff, 1980; Lindgren et al., 1980; Spicer et al., 1980). It would be valuable therefore to ascertain whether the changes in formulation described in this paper are also capable of altering clinical response to pressurized inhalation aerosols.

References

Camner, P. and Philipson, K., Human alveolar deposition of 4 μm Teflon particles. Arch. Environ. Health., 36 (1978) 181–185.

Ellul-Micallef, R., Morén, F., Wetterlin, K. and Hidinger, K.G., Use of a special inhaler attachment in asthmatic children. Thorax, 35 (1980) 620–623.

Lindgren, S.B., Formgren, H. and Morén, F., Improved aerosol therapy of asthma: effect of actuator tube size on drug availability. Eur. J. Resp. Dis., 61 (1980) 56–61.

Lippmann, M. and Albert, R.E., The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. Am. Ind. Hyg. Ass. J., 30 (1969) 257–275.

May, K.R., An improved spinning top homogeneous spray apparatus. J. Appl. Phys., 20 (1949) 932–938.

Morén, F., Drug deposition of pressurized inhalation aerosols. II. Influence of vapour pressure and metered volume. Int. J. Pharm., 1 (1978) 213–218.

Morén, F. and Andersson, J., Fraction of dose exhaled after administration of pressurized inhalation aerosols. Int. J. Pharm., 6 (1980) 295–300.

Newman, S.P., Pavia, D., Morén, F., Sheahan, N.F. and Clarke, S.W., Deposition of pressurized aerosols in the human respiratory tract. Thorax, 36 (1981a) 52–55.

Newman, S.P., Morén, F., Pavia, D., Little, F. and Clarke, S.W., Deposition of pressurized suspension aerosols inhaled through extension devices. Am. Rev. Resp. Dis., 124 (1981b) 317–320.

Newman, S.P., Pavia, D. and Clarke, S.W., How should a pressurized β-adrenergic bronchodilator be inhaled? Eur. J. Resp. Dis., 62 (1981c) 3–20.

Newman, S.P., Pavia, D., Garland, N. and Clarke, S.W., Effects of various inhalation modes on the deposition of radioactive pressurized aerosols. Eur. J. Resp. Dis., 63, Suppl. 119 (1982) 57–65.

Pavia, D. and Thomson, M.L., The fractional deposition of inhaled 2 μm and 5 μm particles in the alveolar and tracheobronchial regions of the healthy human lung. Ann. Occup. Hyg., 19 (1976) 109–114.

Polli, G.P., Grim, W.M., Bacher, F.A. and Yunker, M.H., Influence of formulation on aerosol particle size. J. Pharm. Sci., 58 (1969) 484–486.

Rance, R.W., Studies of the factors controlling the action of hair sprays-III: The influence of particle velocity and diameter on the capture of particles by arrays of hair fibres. J. Soc. Cosmet. Chem., 25 (1974) 545–561.

Ruffin, R.E., Montgomery, J.M. and Newhouse, M.T., Site of beta-adrenergic receptors in the respiratory tract. Chest, 74 (1978) 256–260.

Sanders, P.A., Principles of Aerosol Technology, Van Nostrand Reinhold, London, 1970, pp. 3–7.

Siegel, S., Non-parametric Statistics for the Behavioural Sciences, McGraw-Hill Kogakusha, Tokyo, 1956.

Spicer, J.E., Cayton, R.M., Frame, M. and Winsey, N.J.P., Influence of tube-spacer on aerosol efficacy. Lancet, 2 (1980) 1248.

Tothill, P. and Galt, J.M., Quantitative profile scanning for the measurement of organ radioactivity. Phys. Med. Biol., 16 (1971) 625–634.

Wiener, M.V., How to formulate aerosols to obtain the desired spray pattern. J. Soc. Cosmet. Chem., 9 (1958) 289–297.