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Effect of vapour pressure on the deposition pattern from solution phase metered dose inhalers

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Summary

The pulmonary deposition of ^{99m}Tc-labelled hexamethyl propylene amine oxime, used as a model for propellant soluble drugs, was studied in healthy volunteers using gamma scintigraphy. The radiolabel was delivered using a metered dose inhaler using a low vapour pressure chlorofluorocarbon fill (LVPA, 255 kPa) or a high vapour pressure chlorofluorocarbon fill (HVPA, 448 kPa) in a cross-over design trial. The data showed that a lower proportion of the dose (35%) was swallowed for HVPA compared with LVPA (49%). Within the lung, the proportion of the dose reaching the peripheral airways as determined by the penetration index was the same for both aerosols, although a greater pulmonary deposition of the dose was observed with HVPA. The results obtained confirm previous observations that greater than 40% of the marker achieves pulmonary deposition when dissolved in the propellant phase.

Introduction

Previous work carried out in our laboratory (Ashworth et al., 1991) has shown that the behaviour of propellant-soluble drugs can be modelled using technetium-99m labelled hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) dissolved in chlorofluorocarbon (CFC) propellant mixtures. Deposition studies following administration of a radiolabelled formulation from a metered dose inhaler to healthy volunteers indicate that greater than 40% of dissolved drug can be delivered to the lungs. This compares to the generally quoted figure of 10% for a suspension aerosol (Newman et al., 1982). Although the exact locations of the receptor sites within the lungs for bronchodilators are poorly understood, beta-receptors are thought to be most densely concentrated in 'small' conducting airways (Barnes et al., 1982). Aerosol deposition is critically dependent upon particle size and velocity (Lippmann and Albert, 1969). Drug particles must therefore be small enough i.e.. less than 5 μm diameter, to be

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deposited in the finer airways found towards the periphery of the lung if they are to produce optimal therapeutic effect (Rees et al., 1982). It has long been recognised that raising the vapour pressure will reduce droplet size (Wiener, 1958) and also increase the droplet velocity (Rance, 1974). Although increasing the vapour pressure of the chlorofluorocarbon propellant raises the whole lung deposition of suspended Teflon® particles (Newman et al., 1981), altering the vapour pressure of the propellant blend produces no change in the ratio of peripheral to central deposition of suspended particles (Newman et al., 1982). The effects on dissolved markers clearly merit further investigation.

In the present study, we have extended our previously published investigations (Ashworth et al., 1991) to examine the deposition of ^{99m}Tc-HMPAO, dissolved in the propellant phase from two CFC preparations with vapour pressures of 255 kPa (low vapour pressure aerosol, LVPA) and 448 kPa (high vapour pressure aerosol, HVPA), respectively.

Materials and Methods

A stock solution of technetium-99m labelled hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) in trichlorofluoromethane (propellant 11) was prepared as described previously (Ashworth et al., 1991).

Mixtures of propellants 12 and 114 were prepared in the ratio of 90:5 (HVPA), 60:35 (LVPA) and stored in 20 ml pressurised glass containers. Preweighed aluminium aerosol canisters fitted with an O ring (3M Health Care) and containing Span 85 (67 mg) were chilled on ice and ^{99m}Tc-HMPAO in 0.5 ml propellant added. The glass and aluminium containers were then cooled in liquid nitrogen. The necks of the glass containers were cut and 9.5 ml from the contents of the glass container transferred quantitatively to the aluminium canister. The canister was then fitted with a 50 μl metering head (3M Health Care), crimped and reweighed. The final composition of the mixtures was as follows: HVPA, propellants 12:114:11 in the ratio 90:5:5 and LVPA ratio 60:35:5. Radioactivity of the canister was assayed using an Isotope Assay Calibrator type 238 Ionisation Chamber and Electrometer Unit (D.A. Pitman, Weybridge)

Aerosol characterisation

Size analysis of aerosol droplets was undertaken using an Andersen eight-stage cascade impactor fitted with a glass throat on the first stage. Each aerosol under test was shaken, primed and secured in an inverted position in the oral adaptor. 40 actuations were directed on an airflow of 28.3 l min^{-1} into the cascade impactor before the apparatus was disassembled and the amount of activity at each location determined by scintillation counting. The data are expressed as the percentage deposition in the throat and adaptor together with the amount entering the impactor. The respirable fraction (RF) was calculated from aerosol deposited on the later six stages of the device (i.e., droplets with aerodynamic diameters < 5.8 μm).

Head space pressures were measured using a Bourdon pressure gauge following particle size testing since the test was destructive. All tested had retained greater than 95% of the starting weight indicating that seals remained patent.

Aerosol administration

One group of 11 subjects, six females and five males, participated in each deposition study, the trial being conducted as a cross-over design. The subjects had a mean $\pm$ SD height of 1.70 ± 0.10 m, mean $\pm$ SD weight of 63.59 ± 9.35 kg and a mean $\pm$ SD FEV_1/FVC ratio of $80.73 \pm 8.58\%$; all of which are within the normal range. A pregnancy test was performed using the urine of all female subjects on the morning of every study day. All potential subjects were screened prior to participation in the study. Exclusion criteria included poor general health, abnormal lung function (assessed by an Ohio 840 Spirometer (Airco®)), respiratory problems, any possibility of pregnancy, cigarette smoking and participation in a similar study during the previous 12 months. All subjects gave informed written consent and the studies were approved by the Ethical Committee of Nottingham University Medical School. The

maximum total radiation dose received was 0.2 mSv; the administration of all the radiopharmaceuticals during these investigations was approved by the Department of Health and Social Security Administration of Radioactive Substances Advisory Committee.

Inhalation and imaging of radiolabelled aerosols

Each subject was trained to use a metered dose inhaler containing a placebo canister in the standard method described by Muers (1986) before inhalation of radiolabelled aerosol. The subject was then seated in front of the gamma camera and an ^{81m}Kr ventilation study performed. Inhalation of ^{81m}Kr gas allowed an image of the air space to be detected by the gamma camera. The image was recorded during tidal breathing of the gas delivered via a face mask, with the subject sitting erect in front of the gamma camera (Fazio et al., 1978). Anterior and posterior views were recorded containing 200 000 counts. The canister was shaken and primed by firing two shots before administration of five sequential actuations. This was followed by imaging the distribution of the ^{99m}Tc-HMPAO labelled aerosol. Both anterior and posterior images were again obtained, in this case for 300 s each.

Analysis of imaging data

The relative distributions of the aerosol propellants within the lungs were assessed using quantitative indices applied to the data obtained with the ^{99m}Tc-HMPAO labelled aerosols and the krypton gas (Agnew et al., 1982). Using the posterior image a contour line was drawn representing the outer margins of the lungs as seen on the ^{81m}Kr image (Fig. 1a). A best fit rectangle was drawn around each lung and divided up into a three by four matrix, the width being a multiple of three and the height a multiple of four. Each lung was subsequently divided into a central zone comprising the four inner cells, and a peripheral zone comprising the outer eight cells of each matrix. The peripheral zone corresponds anatomically to the small conducting airways and the alveoli of the lung, whereas the central zone

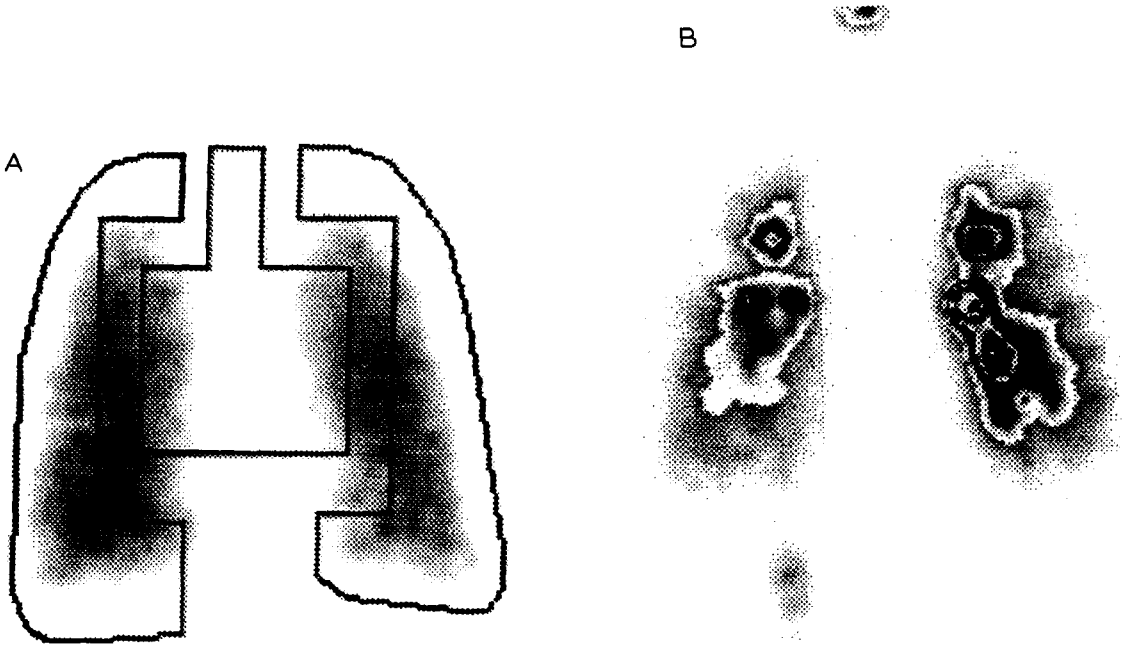

Fig. 1. (a) ^{81m}Kr image showing division of image into an inner and two outer regions of interest. (b) HMPAO image for same subject as in panel a. Note more central deposition compared to the gas image and images of stomach (bottom) and mouthpiece (top)

represents mainly the larger wider airways but also includes some small airways and alveoli. The regions were then superimposed onto the ^{99m}Tc-HMPAO image and additional regions drawn around the oesophagus/trachea, stomach and a boxed area of low background activity (Fig. 1b). Deposition in the stomach is an indicator of marker which has been swallowed. A suitable computer algorithm was used to determine the total number of counts and the average counts per cell in each region of interest and subsequently corrected for background activity. This method of analysis was repeated for all anterior and posterior technetium-99m and ^{81m}Kr images. Each individual's template was used for assessing all aerosol deposition.

Statistical analysis

A geometric mean correction was applied to allow for differences in attenuation of the radiation by overlying tissues. It was calculated by taking the square root of the product of total anterior and total posterior counts in each region. Analysis of deposition was performed on the right lung image only, because the stomach region was noted to overlie the left lung image in some subjects. Regional deposition in the stomach, oesophagus/trachea and each lung was expressed as a percentage of total aerosol deposition. The corrected count rates for each lung were expressed by calculating the 'Penetration Index' (Agnew et al., 1981), a ratio of peripheral to inner zone activity. The data were found to be normally distributed and differences were assessed by the use of a paired Students' *t*-test.

Results

The influence of vapour pressure on aerosol characteristics is shown in Table 1. It is evident that aerosols generated from the lower vapour pressure propellant blend resulted in a significantly higher deposition in the adaptor and throat, with a corresponding reduction in the proportion of the actuated dose entering the impactor, compared to the higher vapour pressure formulation. This can be explained by the lower volatility of the LVPA blend which will result in the formation of larger primary droplets evaporating at a slower rate compared to those generated by the HVPA formulation. Consequently, the respirable fraction emitted from the HVPA was almost two fold greater than those generated by the LVPA.

TABLE 1

The influence of vapour pressure on aerosol characteristics

	Relative deposition (% ± SD, $n = 3$)		$P <$ [a]
	HVPA	LVPA	
Adaptor	23.7 ± 0.70	36.3 ± 3.7	0.01
Throat	23.9 ± 1.20	37.0 ± 5.3	0.025
Impactor	52.4 ± 0.70	26.7 ± 3.6	0.005
Respirable fraction (RF)	51.6 ± 0.6	26.3 ± 3.6	0.01

[a] Differences between HVPA and LVPA parameters were assessed by paired *t*-test.

When the propellant vapour pressure was raised from 255 kPa (LVPA) to 488 kPa (HVPA) whole lung deposition (mean ± SD) rose significantly ($P < 0.05$) in all subjects from 50.9 ± 17.0 to 65.0 ± 10.4%. The ^{81m}Kr image indicated the total ventilatory area of the lungs and approx. 95% of gas was detected in this region. Deposition was determined for central and peripheral right lung regions, oesophagus/trachea and

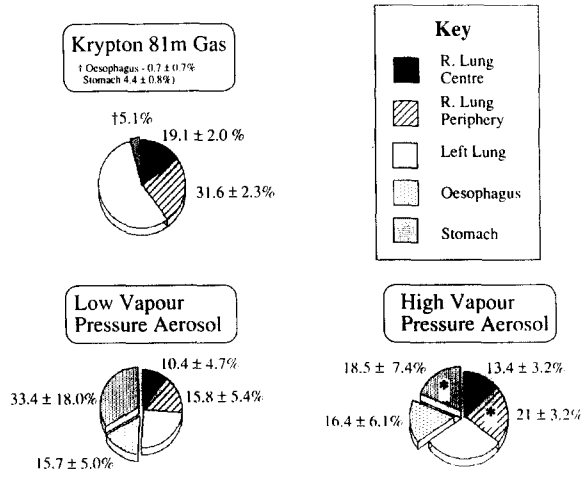

Fig. 2. Pie charts illustrating mean distribution of activity following ^{81m}Kr gas or the high (HVPA) and low (LVPA) vapour pressure aerosols. * Illustrates significant differences between data sets for LVPA and HVPA aerosols (paired *t*-test, $P < 0.05$)

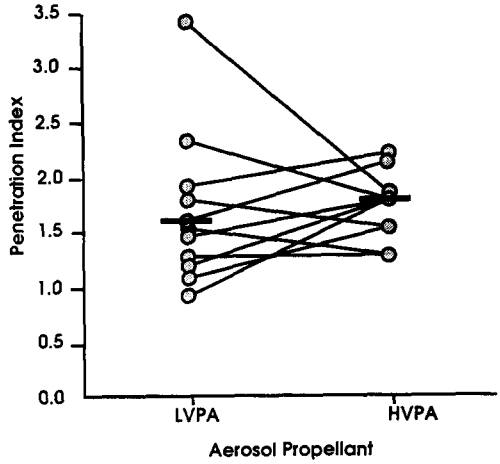

Fig. 3. Penetration indices for the right lung for high (HVPA) and low (LVPA) pressure propellants ($n = 11$; mean $\pm$ SD = 1.6 ± 0.7 for LVPA and 1.8 ± 0.4 for HVPA).

stomach (Fig. 2). The data showed a significant ($P < 0.05$) reduction in the amount of HVPA (35.1%) swallowed compared with LVPA (49.1%).

Within the lung the proportion of the dose reaching the peripheral airways as determined by the 'penetration index' was similar for both aerosols (Fig. 3). It can be seen that the HVPA achieved a more consistent penetration into the periphery compared to LVPA, as reflected by the lower variation in the deposition pattern between individuals.

Discussion

The effectiveness of pulmonary drug delivery from a metered dose inhaler is a function of the amount of drug delivered to the appropriate site in the lung. In general terms, aerosols with a MMAD of 3–5 μm are considered optimal for drug delivery to the upper airways and small bronchi whereas a lower MMAD of 0.8–3 μm is considered optimal for the treatment of parenchymal disease (Aerosol Consensus Committee, 1991). Above 5 μm, oropharyngeal deposition prevents material reaching the lung and the proportion of the dose in this particle size range will be lost by swallowing.

Kim and co-workers (1985) specified four parameters which critically influence the size distribution of the particle cloud from a pressurised aerosol viz: the canister pressure; the physical properties of the propellants including the vapour pressure, density, surface tension, heat of vaporisation of the propellants; the nature of the suspended particulates and finally, the design of the valve and actuator mechanism. When the can is fired, the contents are released through as metering valve and undergo volume expansion. This causes the contents to be released as a mixture of liquid and gas and the high speed gas flow shears the liquid stream breaking the droplets at the orifice. Greater vapour pressure causes higher gas flow velocities and hence more shear force to reduce particle size. The flash evaporation of the solvents proceed at different rates as a function of boiling point The propellants P-11, P-12 and P-114 have boiling points of 23.8, −29.8 and 3.8°C, respectively, and it has been calculated that the droplets associated with P-12 vaporise 10-times faster than those associated with P-11 (Kim et al., 1985). Raising the vapour pressure by the use of more volatile propellants will produce smaller initial droplets with more rapid evaporation (Polli et al., 1969; Wiener, 1958) but they will also have a greater initial velocity (Rance, 1974).

The observed differences in HVPA and LVPA deposition are therefore almost certainly due to the production of a cloud of smaller sized particles with the more volatile propellant. In a conventional metered dose formulation, the drug is in suspension, rather than being in solution but even in this instance higher vapour pressure reduces particle size by breaking up agglomerates. It has been shown that the MMAD of dry isoprenaline particles was reduced from 3.7–4.0 to 1.9–2.5 μm on increasing the head space pressure from 310 to 550 kPa (Porush et al., 1960). Very lipophilic β_2-adrenoreceptor agonists such as tulobuterol can be formulated to dissolve in the propellant and the ^{99m}Tc-HMPAO marker used in our experiments mimics this situation The size distribution of the initial droplets in this study can be calculated using the concentration of non-volatile residual material in solution using the method described by Mercer et al. (1965). From this calculation, it is estimated that the initial particle size (on actuation) of the ^{99m}Tc-

HMPAO aerosols lies in the range 20–30 μm. The LVPA produces a coarser, less volatile aerosol (Table 1). Davies (1973) has calculated that droplets 10 μm in diameter vaporise completely 24-times faster than droplets of 50 μm diameter and thus the initial droplet size has a marked influence on the characteristics of the final aerosol cloud.

Reducing the droplet size should reduce inertial impaction on the oropharynx and consequent deposition in the stomach. Theory predicts that particles larger than 10 μm in diameter will be lost be impaction onto the oropharynx (Marple and Willeke, 1976). In the present study, the stomach deposition was $33.4 \pm 18\%$ from the low vs $18.5 \pm 7.4\%$ from the high vapour pressure aerosol. The difference in the stomach deposition was reflected in a higher pulmonary deposition for HVPA which is agreement with the calculated respirable fraction. ^{81m}Kr distribution showed that 50.7% of the inhaled gas was in the right lung region of interest (ROI). Examining the data for the aerosols with respect to the ^{81m}Kr figures, 52% of LVPA was deposited within the right lung ROI compared to 68% of the marker for the HVPA. Within the lung there is no difference between the fraction of central and peripheral deposition for high and low vapour pressure aerosols. Similar results for suspended particles were obtained by Newman et al. (1982).

The results of this study indicate that a propellant soluble substance should achieve greater pulmonary deposition than a suspended particle and that this deposition can be optimised by raising the head space pressure in the metered dose inhaler. The use of propellant-soluble drugs should therefore be considered in therapy of obstructive lung diseases such as asthma.

References

Aerosol Consensus Committee, Aerosol consensus statement. *Chest,* 100 (1991) 1106–1109.

Agnew, J.E., Pavia, D. and Clarke, S.W., Airways penetration of inhaled radioaerosols: an index to small airways function? *Eur. J. Respir. Dis.,* 62 (1981) 239–255.

Agnew, J.E., Francis, R.A., Pavia, D. and Clarke, S.W., Quantitative comparison of ^{99m}Tc-aerosol and ^{81m}Kr ventilation images. *Clin. Phys. Physiol. Meas,* 3 (1982) 21–30.

Ashworth, H.L., Wilson, C.G., Sims, E.E., Wotton, P. and Hardy, J.G., Delivery of propellant soluble drug from a metered dose inhaler. *Thorax,* 46 (1991) 245–247.

Barnes, P.J., Basbaum, C.B., Nadel, J.A. and Roberts, J.M., Localisation of beta adrenoreceptors in the mammalian lung by light microscopic autoradiography. *Nature,* 299 (1982) 444–447.

Davies, C N., Evaporation of fine atmospheric particles. *Faraday Symp. Chem. Soc.,* 7 (1973) 34–41.

Fazio, F., Lavender, J.P. and Steiner, R.E., ^{81m}Kr ventilation and ^{99m}Tc-perfusion scans in chest disease; comparison with standard radiographs. *Am. J. Resp. Med.,* 130 (1978) 421–428.

Kim, C.S., Trujillo, D. and Sackner M.A., Size aspects of metered dose inhaler aerosols. *Am. Rev. Respir. Dis.,* 132 (1985) 137–142.

Lippman, 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. Assoc. J.,* 30 (1969) 257–275.

Marple V.A. and Willeke, K., Impactor design. *Atmos. Environ.,* 10 (1976) 891–896.

Mercer T.T., Goddard R.F and Flores R.L., Output characteristics of several commercial nebulizers. *Ann. Allergy,* 23 (1965) 314–326.

Muers, M., Uncontrolled asthma. *Mims Magazine,* Feb. (1986) 25–30.

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

Newman, S.P., Moren, F., Pavia, D., Corrado, O. and Clarke, S.W., The effects of changes in metered volume and propellant vapour pressure on the deposition of pressurised inhalation aerosols. *Int. J. Pharm.,* 11 (1982) 337–344.

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.

Porush, I., Theil, C. and Young, J.G., Pressurised pharmaceutical aerosols for inhalation therapy. I: Physical testing methods. *J. Am. Pharm. Assoc.,* 49 (1960) 70–72.

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

Rees, J., Choosing an asthma prophylactic. *Mims Magazine,* 1 (1986) 18–25.

Rees, P.J., Clark T.J.H. and Moren, F., The importance of particle size in response to inhaled bronchodilators. *Eur. J. Respir. Dis.,* 63 (Suppl. 119) (1982) 73–78.

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