International Journal of Pharmaceutics, 74 (1991) 203–208

ADONIS 037851739100291T

IJP 02486

Lung deposition of 5 mg Intal from a pressurised metered dose inhaler assessed by radiotracer technique

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(Received 6 March 1991)
(Accepted 15 April 1991)

Key words: Asthma therapy; Sodium cromoglycate; ^{99m}Tc labeling; Metered dose inhaler; Aerosol deposition

Summary

Deposition from a pressurised metered dose inhaler (MDI) delivering 5 mg sodium cromoglycate (Intal 5, Fisons plc), has been measured by a Tc99m-labelling technique. Ten healthy volunteers inhaled: (i) from a standard MDI at 30 l/min; (ii) from a 10 cm spacer tube (Aerotube) at 30 l/min; and (iii) from the Aerotube at 100 l/min. A mean (SE) 8.8 (1.1) % of the dose was deposited in the lungs from the standard MDI, but this amount was not significantly changed either for slow inhalation (11.3 (1.9) %) or fast inhalation (7.1 (1.3) %) through the spacer. Lung deposition was lower than that observed previously for other canisters delivering smaller amounts of drug per metered dose. Oropharyngeal deposition fell from a mean 79% with standard MDI to a mean 29% with the spacer ($P < 0.05$). It is concluded that a 10 cm tube spacer does not significantly enhance lung deposition of 5 mg Intal in subjects with good inhaler technique, but may reduce the incidence of oropharyngeal irritation, cough and unpleasant taste.

Introduction

Pressurised metered dose inhalers (MDIs) have become the most widespread inhalation devices for the treatment and prophylaxis of asthma, and are popular with patients because of their portability, compactness and convenience. However, there are two major problems with drug delivery from the MDI. Firstly, a high proportion of patients have poor inhaler technique, either because they cannot coordinate actuating the spray with inhalation or because they react to the cold blast of propellants on the back of the throat by stopping inhalation (Crompton, 1982; Pedersen et al., 1986), the so-called 'cold-Freon' effect. Secondly, the majority of the dose is impacted in the oropharynx, even with good technique (Newman et al., 1981a; Vidgren et al., 1987a). This may cause cough and irritation, and oropharyngeal candidiasis and dysphonia may arise in the case of inhaled corticosteroids (Toogood et al., 1984).

A spacer attachment to the inhaler mouthpiece makes the MDI easier to use, since problems with poor coordination and cold Freons are less marked. There is a reduction in oropharyngeal deposition with spacers (Newman et al., 1984;

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Newman et al., 1986), and lung deposition is increased with some models (Vidgren et al., 1987b). Previous measurements of deposition from MDIs have used canisters loaded either with inert radiotracers (Dolovich et al., 1981; Newman et al., 1981a) or with drugs delivered as not more than 1 mg per metered dose (Vidgren et al., 1987a; Newman et al., 1989). We report for the first time the deposition from an MDI of an aerosol formulated to deliver 5 mg sodium cromoglycate per metered dose, and the effects of a 10 cm tube spacer upon the deposition pattern of this aerosol.

Materials and Methods

Radiolabelling technique

Metered dose canisters were radiolabelled by a radiotracer method described previously for use with 1 mg sodium cromoglycate MDIs (Newman et al., 1989). Briefly, Tc99m was extracted out of the aqueous phase in chloroform, and after evaporation of the chloroform in an empty canister by compressed air, the contents of a canister delivering 5 mg sodium cromoglycate (Intal 5, Fisons plc) per metered dose were added at below $-60\,^{\circ}$C, and a valve attached by a crimper. Each metered dose delivered approximately 20 MBq Tc99m plus 5 mg sodium cromoglycate in 100 μl propellant.

The technique was evaluated using a multistage liquid impinger (Bell et al., 1973; Newman et al., 1989), in which drug and radiolabel were collected on a 'throat', 4 impaction stages and a filter, with air drawn through the system at 60 l/min. Material penetrating to stage 3, stage 4 and filter represents predominantly aerosol droplets smaller than 7 μm diameter. The distribution of drug within the impinger was measured for three unlabelled canisters; these canisters were then radiolabelled and the measurements repeated, the distributions of both drug and radioactivity from the labelled canisters being determined as previously described (Newman et al., 1989). These measurements were performed both for MDI alone and for MDI plus 10 cm tube spacer (Aerotube, Fisons plc).

In vivo studies

Ten healthy volunteer subjects took part in the study. Their ages ranged from 26 to 49 years, 5 were male and 5 were female. All had normal lung function (forced expiratory volume in 1 s, FEV1, 84–125% predicted), and none were taking medications of any kind. Informed consent was given in writing, and both the Ethical Practices Sub-Committee of the Hospital and the Administration of Radioactive Substances Advisory Committee (ARSAC) approved the study.

Each subject performed an aerosol inhalation from the labelled MDIs on 3 days in a randomised order. These inhalations involved: (i) standard MDI actuator, inhaled flow rate 30 l/min; (ii) MDI plus 10 cm tube spacer (Aerotube), inhaled flow rate 30 l/min; and (iii) MDI plus Aerotube, inhaled flow rate 100 l/min. A single metered dose was actuated by an observer during a deep breath with a subsequent breath-holding pause of 10 s, and exhalation was made via a low-resistance filter. The inhalation mode for the standard MDI represented correct or optimal MDI technique. Prior to inhalation, subjects practiced with a placebo canister until their inhalation was judged to be adequate. Inhalation was monitored by a modified Vitalograph Compact spirometer, which gave a record of inhaled volume, inhaled flow rate and breath-holding pause. Lung function tests (FEV1, forced vital capacity (FVC), peak expiratory flow rate (PEFR) and maximum mid-expiratory flow rate (MMFR)) were measured prior to aerosol inhalation on each study day; these were compared with European Community Coal and Steel predicted normal values (Quanjer et al., 1983).

Radioactivity in the lungs and oropharynx was monitored immediately after inhalation by an Ohio Nuclear 110 gamma camera connected online to a Nodecrest data processing system, counts being corrected for gamma-ray attenuation in tissue. The percentages of the dose deposited on the actuator, spacer and exhaled air filter were assessed by comparing their counts as measured by probe counters with those from a calibration dose collected on a further filter. Radioactivity not appearing in these samples was assumed to be in the body and was divided into lung and

TABLE 1

Percentages of untreated sodium cromoglycate, chloroform-treated sodium cromoglycate and radiolabel within a multistage liquid impinger [a]

	Untreated drug (mean (SE))	Treated drug (mean (SE))	Radiolabel (mean (SE))
MDI alone			
Actuator	8.6 (0.4)	5.6 (3.3)	14.1 (4.9)
Throat	37.0 (4.8)	40.4 (6.0)	38.3 (4.6)
Stage 1	32.7 (4.0)	33.6 (6.1)	25.9 (5.6)
Stage 2	8.9 (0.2)	8.7 (2.5)	9.1 (3.3)
Stage 3	6.3 (0.9)	6.8 (1.4)	6.3 (1.4)
Stage 4	5.9 (0.4)	4.7 (0.4)	5.9 (1.1)
Filter	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)
MDI plus spacer			
Actuator	7.1 (0.6)	9.5 (2.2)	11.9 (3.4)
Spacer	39.2 (3.0)	43.9 (2.1)	47.5 (1.9)
Throat	7.0 (1.9)	7.2 (0.3)	7.5 (0.4)
Stage 1	21.3 (3.2)	14.8 (3.0)	12.4 (4.0)
Stage 2	8.4 (1.3)	9.3 (2.1)	6.6 (0.3)
Stage 3	7.2 (2.1)	6.8 (1.9)	6.4 (0.8)
Stage 4	9.2 (1.5)	8.1 (1.1)	7.3 (1.4)
Filter	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)

[a] $n = 3$.

oropharyngeal fractions according to the tissue-corrected gamma camera counts.

On one of the study days, a Kr81m ventilation scan was performed, and this was used to determine the percentages of the dose in central, intermediate and peripheral zones, as previously described (Newman et al., 1989). We estimate that the radiation dose to the lungs from three inhalations of Tc99m and one inhalation of Kr81m is approximately 200 μGy (20 mrad).

The deposition data for the three studies were analysed using the Friedman test of analysis of variance by ranks, and where a significant result ($P < 0.05$) was found, pairs of data were tested by

TABLE 2

Fractionation of the dose between lungs, oropharynx, apparatus and exhaled air, and regional lung deposition for the 3 studies

	MDI (mean (SE))	Spacer (slow flow) (mean (SE))	Spacer (fast flow) (mean (SE))
% of dose located in:			
Lungs	8.8 (1.1)	11.3 (1.9)	7.1 (1.3) [b]
Oropharynx	79.5 (2.2)	29.5 (2.3) [a]	29.3 (3.0) [a]
Actuator/spacer	11.4 (1.3)	59.1 (2.7) [a]	63.5 (4.0) [a]
Exhaled air	0.3 (0.1)	0.1 (0.1)	0.1 (0.1)
Regional deposition			
Peripheral zone (% of dose)	4.4 (0.5)	5.5 (0.8)	3.2 (0.5) [b]
Peripheral/central ratio	1.91 (0.14)	1.86 (0.16)	1.44 (0.12) [a]

[a] $P < 0.05$ compared to MDI.

[b] $P < 0.05$ for slow vs fast flow via spacer.

the multiple comparison technique of Conover (1980).

Results

Evaluation of radioaerosol technique

The distributions of untreated drug, of drug treated with chloroform plus Tc99m, and of radiolabel were very similar (Table 1). With the standard MDI, a mean 12.6% of the untreated drug penetrated beyond stage 2, compared to 11.9% of treated drug and 12.6% of the radiolabel. With the MDI plus spacer, these figures were 16.9%, 15.3% and 14.1%, respectively.

Fractionation of dose in vivo

The fractionation of the dose in vivo between lungs, oropharynx, apparatus and exhaled air is shown in Table 2. A significantly ($P < 0.05$) higher percentage of the dose was found in the lungs for slow inhalation via the Aerotube (mean 11.3%) compared to fast inhalation (mean 7.1%, $P < 0.05$). However, the percentage of the dose deposited in the lungs for the standard MDI (mean 8.8%) was intermediate and did not differ significantly from that in either study with the Aerotube.

Deposition on the apparatus increased from a mean 11.4% of the dose for the standard MDI to about 60% with the Aerotube ($P < 0.05$), while deposition in the oropharynx decreased from 79.5% with the MDI to about 30% with the Aerotube ($P < 0.05$). With the spacer, neither deposition on the apparatus nor deposition in the oropharynx varied significantly according to the inhaled flow rate.

The percentage of the dose in peripheral lung (Table 2) was significantly ($P < 0.05$) higher for slow inhalation via the Aerotube than for fast inhalation, with the deposition for the standard MDI having an intermediate value. The peripheral/central zone ratio was significantly ($P < 0.05$) higher for the MDI than for fast inhalation via the Aerotube.

Inhalation details and lung function

The inhaled volume, averaged inhaled flow rate and breath-holding pause during aerosol inhalation are listed in Table 3. Inhaled flow rate was significantly higher with fast inhalation through the Aerotube ($P < 0.001$), but otherwise inhalation modes were similar on the 3 study days. Lung function values were also similar on each study day (Table 3).

Discussion

The deposition pattern of pressurized aerosols was largely unknown for over 20 years, other than from indirect assessments based upon pharmacokinetic studies (Davies, 1975). Direct measurements using gamma labelling techniques were developed in the 1980s; these have utilised inert solid particles (Newman et al., 1981a), inert liquid droplets (Dolovich et al., 1981), or active drugs in doses not exceeding 1 mg (Short et al., 1981; Vidgren et al., 1987a; Köhler et al., 1988; Newman et al., 1989). The deposition of aerosol from

TABLE 3

Details of inhalation modes and lung function on each study day

	MDI (mean (SE))	Spacer (slow flow) (mean (SE))	Spacer (fast flow) (mean (SE))
Inhaled volume (l)	2.77 (0.23)	2.70 (0.12)	2.50 (0.20)
Average inhaled flow rate (l/min)	27.8 (1.5)	28.9 (1.4)	94.2 (4.0)
Breath-holding (s)	8.8 (0.4)	9.2 (0.3)	9.7 (0.5)
FEV 1 (l)	3.61 (0.18)	3.62 (0.20)	3.59 (0.19)
FVC (l)	4.54 (0.16)	4.52 (0.18)	4.45 (0.16)
PEFR (l/min)	600 (24)	582 (30)	563 (34)
MMFR (l/s)	3.80 (0.46)	3.93 (0.50)	3.98 (0.49)

a metered dose inhaler delivering 5 mg of drug per metered dose has not previously been measured. The technique used in the present study does not involve direct chemical labelling of the drug substance, but rather an association between the radionuclide Tc99m and sodium cromoglycate in the inhaler. In vitro studies with the multistage liquid impinger showed firstly that the addition of radionuclide to canisters containing the drug had little effect on the droplet size spectrum, and secondly that the radiolabel acted as a marker for the presence of drug across a range of droplet sizes.

In these studies, a mean of 8.8% of the dose was deposited in the lungs using correct inhaler technique from the standard MDI, with 80% deposited in the oropharynx. This figure may be compared with those obtained using analogous techniques and similar inhalation modes for other inhalers delivering smaller amounts of drug per metered dose: the percentages of the dose deposited in the lungs were 11.8% (Newman et al., 1989) and 18.8% (Newman et al., 1990) for correctly used MDIs delivering 1 mg and 100 μg drug per metered dose respectively, and suggests that there is an inverse relationship between drug mass and respirable dose. The spray from a 'suspension' MDI consists of propellant droplets within which the drug particles are enclosed; an increase in the drug concentration may result in the inclusion of multiple drug particles in each propellant droplet and hence in an increase in aerosol size because of the formation of clusters or aggregates in the spray (Gonda et al., 1985; Dalby and Byron, 1988). This would increase oropharyngeal deposition and reduce penetration into the bronchial tree. A change in drug concentration in an experimental MDI was found to alter the site of aerosol deposition in excised dog lungs (Sweeney et al., 1990). However, an increase in amount of drug per metered dose is often accompanied by an increase in metering volume, which may in itself alter the deposition pattern (Newman et al., 1982). The practical consequence for Intal MDIs is that an inhaler delivering 5 mg of sodium cromoglycate (metering volume 100 μl) will deposit approximately 4 times more drug in the lungs per metered dose than an inhaler which delivers 1 mg (metering volume 50 μl).

There was a significant increase in deposition in the lungs with slow inhalation through the Aerotube compared to fast inhalation. A bronchodilator aerosol inhaled through a tube spacer by asthmatic children was more efficacious with slow inhalation (Pedersen, 1985). Although there was a trend towards improved lung deposition for the Aerotube with slow inhalation compared to the standard MDI, this was not significant; this finding was also noted in an earlier study with another tube spacer (Newman et al., 1981b). Hence the Aerotube is unlikely to play a role as a means of markedly improving deposition in the lungs of 5 mg Intal in patients with good inhalation technique, and might even reduce deposition in the lungs if it was used with rapid inhalation. However, tube spacers can act as useful coordination aids in patients with poor inhaler technique (Godden and Crompton, 1981). Additionally, the Aerotube reduced oropharyngeal deposition markedly, and might be a useful means of reducing oropharyngeal irritation, cough and unpleasant taste that is sometimes reported with 5 mg Intal inhalers. The fractionation of the dose between lungs, oropharynx and spacer varies according to the model of spacer used (Vidgren et al., 1987b), and hence another design of spacer device might enhance the deposition of 5 mg Intal in the lungs compared to that from a standard MDI.

In conclusion, therefore, the percentage of the dose deposited in the lungs from a 5 mg Intal canister is less than that delivered from other canisters. The addition of a small tube spacer device (Aerotube) is unlikely to enhance significantly drug delivery in patients with good inhaler technique.

Acknowledgement

We are grateful to J. Beckhelling of the Statistics Department, Fisons plc Pharmaceutical Division, for performing the statistical analysis.

References

Bell J.H., Brown, K. and Glasby, J., Variation in delivery of isoprenaline from various pressurized inhalers. *J. Pharm. Pharmacol.*, 25, Suppl. (1973) 32P–36P.

Conover, W.J., *Practical Non-Parametric Statistics*. Wiley, New York, 1980, p. 300.

Crompton, G.K., Problems patients have using pressurised aerosol inhalers. *Eur. J. Respir. Dis.*, 63, Suppl. 119 (1982) 57–65.

Dalby, R.N. and Byron, P.R., Comparison of output particle size distributions from pressurised aerosols formulated as solutions or suspensions. *Pharm. Res.*, 1 (1988) 36–39.

Davies, D.S., Pharmacokinetics of inhaled substances. *Postgrad. Med. J.*, 51, Suppl. 7 (1975) 69–75.

Dolovich, M.B., Ruffin, R.E., Roberts, R. and Newhouse, M.T., Optimal delivery of aerosols from metered dose inhalers. *Chest*, 80, Suppl. (1981) 911–915.

Godden, D.J. and Crompton, G.K., An objective assessment of the tube spacer in patients unable to use a conventional pressurised aerosol efficiently. *Br. J. Dis. Chest*, 75 (1981) 165–168.

Gonda, I., Development of a systematic theory of suspension inhalation aerosols, I. A framework to study the effects of aggregation on the aerodynamic behaviour of drug particles. *Int. J. Pharm.*, 27 (1985) 99–110.

Köhler, D., Fleischer, W. and Matthys, H., A new method for easy labelling of beta-2 agonists in the metered dose inhaler with Tc99m. *Respiration*, 53 (1988) 65–73.

Newman, S.P., Pavia, D., Morén, F., Sheahan, N.F. and Clarke, S.W., Deposition of pressurised 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 pressurised suspension aerosols inhaled through extension devices. *Am. Rev. Respir. Dis.*, 124 (1981b) 317–320.

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

Newman, S.P., Millar, A.B., Lennard-Jones, T.R., Morén, F. and Clarke, S.W., Improvement of pressurised aerosol deposition with Nebuhaler spacer device. *Thorax*, 39 (1984) 935–941.

Newman, S.P., Woodman, G., Clarke, S.W. and Sackner, M.A., Effect of InspirEase on the deposition of metered dose aerosols in the human respiratory tract. *Chest*, 89 (1986) 551–556.

Newman, S.P., Clark, A.R., Talaee, N. and Clarke, S.W., Pressurised aerosol deposition in the human lung with and without an 'open' spacer. *Thorax*, 44 (1989) 706–710.

Newman, S.P., Weisz, A. and Clarke, S.W., Bronchodilator delivery from Gentle-Haler, a new low-velocity pressurized aerosol inhaler. *Am. Rev. Respir. Dis.*, 141 (1990) A18.

Pedersen, S., Optimal use of tube spacer aerosols in asthmatic children. *Clin. Allergy*, 15 (1985) 473–478.

Pedersen, S., Frost, L. and Arnfred, T., Errors in inhalation technique and efficiency in inhaler use in asthmatic children. *Allergy*, 41 (1986) 118–124.

Quanjer, P.H., Standardised lung function testing. *Bull. Eur. Physiopathol. Respir.*, 19, Suppl. 5 (1983) 7–95.

Short, M.D., Singh, C.A., Few, J.D., Studdy, P.T., Heaf, P.J.D. and Spiro, S.G., The labelling and monitoring of lung deposition of an inhaled synthetic anticholinergic bronchodilating agent. *Chest*, 80, Suppl. (1981) 918–921.

Sweeney, T.D., Blanchard, J.D., Carter, J.E., Vadas, E. and Brain, J.D., Changing drug concentration in a metered dose inhaler: does it alter the site of particle deposition in excised dog lungs? *Am. Rev. Respir. Dis.*, 141 (1990) A522.

Toogood, J., Baskerville, J., Jennings, B., Lefcoe, N.M. and Johansson, S.A., Use of spacers to facilitate inhaled corticosteroid treatment in asthma. *Am. Rev. Respir. Dis.*, 129 (1984) 723–729.

Vidgren, M., Karkkainen, A., Karjalainen, P. and Paronen, P., A novel labelling method for measuring the deposition of drug particles in the respiratory tract. *Int. J. Pharm.*, 37 (1987a) 239–244.

Vidgren, M.T., Paronen, P., Karkkainen, A. and Karjalainen, P., Effect of extension devices on drug deposition from inhalation aerosols. *Int. J. Pharm.*, 39 (1987b) 107–112.