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Effect of different modes of inhalation on drug delivery from a dry powder inhaler

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Summary

Although the Spinhaler has been available for many years as a delivery device for sodium cromoglycate powder, the quantity of powder delivered to the lungs and the optimal mode of inhalation for this device have remained largely unknown. Lung deposition of 20 mg sodium cromoglycate powder (labelled with the radionuclide ^{99m}Tc) from the Spinhaler has been measured in 10 healthy volunteers who inhaled by four carefully controlled inhalation modes, involving fast (120 l min^{-1}) and slow (60 l min^{-1}) peak inhaled flow rates, holding the head in the normal and tilted-back (60° to the horizontal) positions, and breath-holding pauses of 0 and 10 s. Inhalation at 60 l min^{-1} significantly ($P < 0.001$) reduced deposition in the lungs compared to inhalation at 120 l min^{-1}. Among the inhalation modes tested, delivery to the lungs was optimised (mean 17.1% of the dose) when powder was inhaled at 120 l min^{-1}, with the head in the normal position, and with 10 s breath-holding.

Introduction

The Spinhaler (Fisons PLC) was introduced 20 years ago (Bell et al., 1971) as a totally novel inhalation device for the delivery of the anti-asthma agent sodium cromoglycate (Intal) (Howell and Altounyan, 1967; Cox, 1969). The Spinhaler offers several advantages compared to the pressurised metered dose inhaler (MDI): first, the dose of 20 mg sodium cromoglycate in a gelatine capsule is larger than that which can be delivered as a single puff from an MDI; second, the Spinhaler is breath-actuated, and can be used successfully by many patients with poor MDI technique (Crompton, 1990); and third no environmentally damaging chlorofluorocarbon propellants are used (Newman, 1990).

Apart from data derived from pharmacokinetic studies (Davies, 1975; Fuller and Collier, 1983; Auty et al., 1987) and from in vitro particle size analysis (Smith et al., 1980), little was known for many years about drug delivery from the Spinhaler. Recently, the radioaerosol studies of Vidgren et al. (1988) showed that only about 10% of the dose is deposited in the lungs, as in the case of the MDI. In order to determine the optimal mode of inhalation for the Spinhaler, we have assessed the effects of inhaled flow rate,

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head position and breath-holding pause on the deposition pattern of radiolabelled sodium cromoglycate powder.

Materials and Methods

Radiolabelling method

A new radiolabelling method involving the radionuclide ^{99m}Tc (gamma ray energy 140 keV, physical half-life 6 h), was devised in order to measure deposition from a Spinhaler, and was based on that described previously for use with the terbutaline sulphate Turbuhaler (Newman et al., 1989a, 1991). 3 ml of eluate from a ^{99m}Tc generator, containing approx. 5 GBq ^{99m}Tc, was mixed with two drops of ammonia and two drops of tetraphenyl arsonium chloride from a fine needle, and with 3 ml chloroform. This mixture was passed through a Whatman 1ps phase-separating filter. The filtrate, containing approx. 2.5 GBq ^{99m}Tc, was topped up to 10 ml with chloroform, and was added to 1 g of micronised sodium cromoglycate powder which had been pelletised into visible spheres of diameter approx. 0.5 mm. After shaking in an ultrasonic bath to suspend the drug spheres uniformly, the chloroform was gently evaporated by compressed air in a fume cupboard. The dried powder was passed through a fine mesh sieve (150 μm), and then transferred to a small glass vial, which was tumbled on a roller for 15 min to reconstitute the drug spheres. Each of a series of gelatine capsules was then filled with 20 mg of the labelled powder, containing 50 MBq ^{99m}Tc.

Evaluation of radiolabelling method

The extent to which the ^{99m}Tc label acted as a marker for the presence of drug was assessed in vitro by a multistage liquid impinger (Bell et al., 1971; Newman et al., 1989a,b) in which aerosol particles are fractionated according to size on a series of glass impaction stages, a 90° bend ('throat') upstream of the first impaction stage, and a filter placed between the impinger and a suction pump. Particles penetrating beyond stage 2 of the impinger represent primarily 'respirable' particles smaller than about 7 μm diameter. These measurements were made at flow rates of 60 and 120 l min^{-1}; at 60 l min^{-1}, the filter was connected to the outlet from stage 4, while at 120 l min^{-1}, the 4th stage was by-passed, with the filter being connected to the outlet from stage 3, since the high resistance of the air inlet to stage 4 prevents a flow rate of 120 l min^{-1} being attained if the impinger is used in its normal fashion.

TABLE 1

In vitro assessment of radiolabelling technique

	At 60 l min^{-1}		At 120 l min^{-1}	
	Drug	Radiolabel	Drug	Radiolabel
Device [a]	38.2 (3.8)	29.9 (1.5)	8.8 (2.5)	24.8 (1.9)
Throat	6.7 (0.4)	12.0 (0.9)	7.0 (0.6)	12.1 (1.0)
Stage 1	37.8 (3.8)	33.8 (1.8)	35.7 (4.3)	29.3 (2.1)
Stage 2	7.3 (1.1)	9.4 (0.7)	10.1 (0.8)	11.9 (1.1)
Stage 3	4.6 (0.4)	7.0 (0.8)	9.6 (0.7)	9.7 (0.9)
Stage 4	5.0 (0.7)	7.3 (1.1)	–	–
Filter	0.5 (0.1)	0.7 (0.1)	8.8 (1.6)	12.1 (1.1)

Values expressed as mean (SE, $n = 8$) percentage distributions of drug and radiolabel in inhalation device and impinger at flow rates of 60 and 120 l min^{-1}.

[a] Denotes retained in Spinhaler and capsule.

Prior to the in vivo experiments, distributions of both drug and radiolabel were obtained from eight capsules at each flow rate, the capsules being prepared as four batches on separate days. The distribution within the Spinhaler and capsule, and within the impinger system, was determined by gamma camera. After 48 h to allow for complete radioactive decay of the radionuclide, the Spinhaler, capsule and impinger were washed out with distilled water, and quantities of sodium cromoglycate in the washings were determined by ultraviolet spectrophotometry. The drug and radiolabel distributions were similar (Table 1), indicating that the deposition of radionuclide in vivo could be used to infer the deposition of sodium cromoglycate. At a flow rate of 120 l min^{-1}, 18.4% of drug and 21.8% of radiolabel, respectively, were found in respirable particles. At a flow rate of 60 l min^{-1} this agreement was less precise, with the respirable fraction comprising a mean 10.1% of the drug and 15.0% of the radiolabel.

Subjects studied

In vivo radioaerosol studies were performed in 10 healthy non-smoking volunteer subjects (six males, four females, age range 23–50 years). All had normal lung function, as assessed by Vitalograph Compact Spirometer, measured values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEFR) and maximum mid-expiratory flow rate (MMFR) being compared with predicted reference values. The subjects' FEV1s ranged from 88 to 112% of the predicted values. Permission to undertake the study was obtained from both the Ethical Practices Sub-Committee of the Royal Free Hospital, and the Administration of Radioactive Substances Advisory Committee. Each subject gave informed consent in writing.

Modes of inhalation

Each subject performed four studies with a different mode of inhalation, on 4 separate days at least 48 h apart, in a randomised order (Table 2). The standard inhalation manoeuvre for using the Spinhaler involves a rapid inhalation (peak inhaled flow rate, PIFR, 120 l min^{-1}) with the head tilted backwards through approx. 60° during inhalation, plus a breath-holding pause of 10 s. The study was designed to test the effects on deposition of the following changes to this standard inhalation manoeuvre (mode A): slow inhalation at PIFR 60 l min^{-1} (mode B), head in the normal position during inhalation (mode C), and no breath-holding pause (mode D).

Inhalation was monitored by a modified Vitalograph Compact Spirometer connected in series with the Spinhaler, which enabled PIFR, inhaled volume and breath-holding pause to be registered. The Spirometer was placed so that the screen could be seen during inhalation, and subjects were required to 'target' their PIFR by following cursors on the screen. Practice inhalations were performed prior to inhalation of the radiolabelled dose until subjects were adjudged to have mastered the required technique. All inhalations began at functional residual capacity, and subjects were instructed to inhale to total lung capacity with the mouthpiece held firmly between closed lips. Exhalations were made via a low resistance filter (Pall Ultipor).

TABLE 2

Modes of inhalation via the Spinhaler

Mode	A	B	C	D
Nominal PIFR (l min^{-1})	120	60	120	120
Head position	tilted	tilted	normal	tilted
Breath-hold (s)	10	10	10	0

Deposition measurements

Immediately after inhalation, a lateral view of the oropharynx (30 s) and a posterior-anterior view of the lungs (100 s) were taken by an Ohio 110 gamma camera coupled to a Nuclear Diagnostic data processing system. Counts were corrected for the attenuation of gamma-rays during their passage to the detector (Newman et al., 1989a,b). The percentages of the dose retained in the capsule and Spinhaler, and on the exhaled air filter, were determined by comparing the count rates in these items with those in an unused capsule, corrections being made for the relative amounts of activity contained in this capsule and the amount originally contained in the capsule that the subject received. The dose was thus fractionated into amounts in (a) lungs, (b) oropharynx, (c) capsule and Spinhaler and (d) exhaled air. The lung fields were divided into central, intermediate and peripheral zones, as described in previous studies (Newman et al., 1989a,b, 1991) and an aerosol penetration index was calculated as the ratio of peripheral zone and central zone depositions.

Statistical tests

The percentage of the administered dose at each site was compared among the four study days using the Friedman non-parametric analysis of variance by ranks, and where a significant difference was found, paired comparisons were made using the Wilcoxon matched-pairs signed-rank test (Siegel and Castellan, 1988). All tests were two-tailed and a P value of 0.05 was taken to indicate statistical significance.

Results

The variable having the most marked effect on deposition patterns was the PIFR (Table 3). The percentage of the dose deposited in the lungs following inhalation at 60 l min^{-1} (mean 5.5%) was significantly less than that for all three study days at 120 l min^{-1} ($P < 0.001$). With inhalation at 120 l min^{-1}, the percentage of the dose deposited in the lungs was maximised when the head was held in the normal position (mean 17.1%, $P < 0.05$ compared to the other two days at this inhaled flow rate). The addition of breath-holding to fast inhalation with the head tilted did not significantly change whole lung deposition.

Both peripheral zone and central zone depositions were increased significantly by inhalation at a PIFR of 120 l min^{-1} ($P < 0.01$), but there were no significant differences in aerosol penetration index among the four study days (Table 3).

The amount of radiolabel recovered in exhaled air was significantly decreased by the addition of a breath-holding pause to the fast inhalation manoeuvre ($P < 0.05$, Table 3), although even when a breath-holding pause was maintained, the mean percentage of the dose exhaled was only 1.0%.

TABLE 3

Percentage of dose deposited at different sites, together with exhaled aerosol and penetration index with various inhalation manoeuvres

Mode	A	B	C	D
Lungs	13.1[c] (3.7–22.1)	5.5 (1.6–9.7)	17.1[bc] (7.8–28.3)	12.3[c] (6.6–21.1)
Oropharynx	57.3 (29–84)	58.5 (44–81)	47.8 (24–75)	51.4 (25–73)
Device [a]	29.4 (4–60)	35.6 (9–53)	34.6 (15–63)	35.3 (17–71)
Exhaled air	0.3 (0.1–0.7)	0.4 (0.1–1.0)	0.6 (0.1–2.4)	1.0 (0.1–2.0)
Penetration index	1.70 (0.9–2.3)	1.37 (0.8–2.3)	1.49 (0.8–2.1)	1.27 (0.7–2.0)

Mean values are given with ranges in parentheses.
[a] Denotes retained in Spinhaler and capsule.
[b] $P < 0.05$ compared with modes A and D.
[c] $P < 0.001$ compared with mode B.

TABLE 4

Inhaled volumes, PIFRs and breath holding pauses for four inhalation modes via the Spinhaler

Mode	A	B	C	D
Inhaled volume (l)	2.78 (1.7–4.0)	2.94 (2.0–4.2)	2.86 (2.2–4.1)	2.59 (1.7–4.9)
PIFR (l min^{-1})	119.9 (107–130)	62.8 (58–71)	120.4 (106–128)	117.9 (110–132)
Breath-hold (s)	9.7 (8.3–10.9)	9.6 (9.0–10.1)	9.3 (8.1–10.5)	N/A

Mean values are given with ranges in parentheses.

The percentage of the dose retained in the Spinhaler and capsules was highly variable, and neither this quantity nor the percentage of the dose deposited in the oropharynx varied significantly among the study days (Table 3).

As shown in Table 4, inhaled volumes were similar on each study day. PIFRs and breath-holding pauses were close to targeted values.

Discussion

These studies have confirmed the results of Vidgren et al. (1988), who showed that only a small percentage of the dose from a Spinhaler is delivered directly to the lungs, with the remainder divided between quantities deposited in the oropharynx and retained in the device itself. However, the data of Vidgren et al. were obtained using spray dried particles of sodium cromoglycate, which differ in both their particle size distribution and flow properties compared to micronised particles which were used in the present study and which are found in commercially available formulations (Vidgren et al., 1987); this could have led to differences in aerosol deposition patterns. As shown in other deposition studies using a variety of inhalation devices, there is a large inter-subject variation in deposition, even when the inhalation manoeuvre is carefully controlled (Dolovich et al., 1983; Newman et al., 1989a,b, 1991; Zainudin et al., 1990). This variation is to be expected whenever the major mechanism of deposition is inertial impaction, as is normally the

case for therapeutic aerosol systems, and reflects inter-subject variability in local anatomy and air flow patterns in the upper airways.

Amongst the inhalation modes which we studied, drug delivery to the lungs from the Spinhaler was optimised by a rapid inhalation (at a PIFR of 120 l min^{-1}) with the head held in the normal position, and with a subsequent 10 s breath-holding pause. Inhalation at a PIFR of 60 l min^{-1} dramatically reduced the amount of radioaerosol detected in the lungs, even though we may have overestimated drug delivery to the lungs at this flow rate owing to the imperfect match between drug and radiolabel size distributions. Other powder inhalers also function optimally with rapid inhalation, reduced drug delivery with slow inhalation via Rotahaler (Pedersen, 1986), Berotec inhaler (Groth and Dirksen, 1983; Pedersen and Steffersen, 1986) and Turbuhaler (Pedersen et al., 1990; Newman et al., 1991) having been demonstrated previously. Breath-holding may not be essential to the optimal inhalation manoeuvre, however. We did not assess the effects of breath-holding upon deposition with the head held in the normal position, but when the head was tilted, breath-holding did not significantly improve deposition in the lungs. Auty et al. (1987) assessed the blood levels of sodium cromoglycate following inhalation from the Spinhaler, and concluded that these were optimised by a combination of fast inhalation and breath-holding. By contrast, the addition of a 10 s breath-holding pause to rapid inhalation did not improve the efficacy of bronchodilators inhaled from Rotahaler (Pedersen, 1986), Berotec inhaler (Pedersen and Steffersen, 1986) or Turbuhaler (Hansen and Pedersen, 1989).

The current Spinhaler leaflet advises patients to tilt the head back during inhalation. This manoeuvre is intended to make a straighter path for the drug particles into the lungs, which should in theory result in less impaction in the oropharynx (Agnew, 1984). However, studies involving both powder inhalers (Pedersen, 1986; Pedersen and Steffersen, 1986; Hansen and Pedersen, 1989) and pressurised aerosols (Pedersen, 1985) have failed to demonstrate any advantage of tilting the head during inhalation. In the present study, significant head tilting reduced lung deposition of sodium cromoglycate compared to holding the head in the normal position, suggesting that the upper airways are narrowed during the extremes of head tilting, perhaps because of changes induced in the shape of the larynx, pharynx or soft palate.

Although the present study was performed in healthy volunteers, we would not expect that results for total lung deposition would differ greatly in patients adopting the same inhalation modes. These would often be patients with relatively mild airways obstruction, taking sodium cromoglycate for prophylaxis. However, the regional deposition patterns within the lungs in patients with airways obstruction may differ from those observed in healthy volunteers (Melchor et al., 1993). Data are lacking, however, on the ability of patients with differing degrees of airway obstruction to attain a flow rate of 120 l min^{-1} through the Spinhaler. Previous studies have shown that adequate flow rates can be achieved through other powder inhalers by most asthmatics (Engel et al., 1990), with the possible exception of very young children and those with acute wheeze (Pedersen, 1986; Pedersen and Steffersen, 1986; Engel et al., 1990).

References

Agnew, J.E., Physical properties and mechanisms of deposition of aerosols. In Clarke, S.W. and Pavia, D. (Eds), *Aerosols and the Lung*, Butterworths, London, 1984, pp. 49–70.

Auty, R.M., Brown, K., Neale, M.G. and Snashall, P.D., Respiratory tract deposition of sodium cromoglycate is highly dependent upon technique of inhalation using the Spinhaler. *Br. J. Dis. Chest*, 81 (1987) 371–380.

Bell, J.H., Hartley, P.S. and Cox, J.S.G., Dry powder aerosols I: a new powder inhalation device. *J. Pharm.Sci.*, 10 (1971) 1559–1564.

Cox, J.S.G., Disodium cromoglycate in asthma. *Br. Med. J.*, 3 (1969) 177.

Crompton, G.K., The adult patient's difficulties with inhalers. *Lung*, 168 (Suppl.) (1990) 658–662.

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

Dolovich, M.B., Ruffin, R., Corr, D. and Newhouse, M.T., Clinical evaluation of a new demand-inhalation MDI aerosol delivery device. *Chest*, 84 (1983) 36–41.

Engel, T., Heinig, J.H., Madsen, F. and Nikander, K., Peak inspiratory flow rate and inspiratory vital capacity of patients with asthma measured with and without a new dry powder inhaler device (Turbuhaler). *Eur. Respir. J.*, 3 (1990) 1037–1041.

Fuller, R.W and Collier, J.K., The pharmacokinetic assessment of sodium cromoglycate. *J. Pharm. Pharmacol.*,35 (1983) 289–292.

Groth, S. and Dirksen, H., Optimal inhalation procedure for the fenoterol powder inhaler. *Eur. J. Respir. Dis.*, 64 (Suppl. 130) (1983) 17–24.

Hansen, O.R. and Pedersen, S., Optimal inhalation technique with terbutaline Turbuhaler. *Eur. Respir. J.*, 2 (1989) 637–639.

Howell, J.B.L. and Alyounyan, R.E.C., A double-blind trial of sodium cromoglycate in the treatment of allergic bronchial asthma. *Lancet*, ii (1969) 539–542.

Melchor, R., Biddiscombe, M.F., Mak, V.H.F., Short, M.D. and Spiro, S.G., Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. *Thorax*, 48 (1993) 506–511.

Newman, S.P., Metered dose pressurised aerosols and the ozone layer. *Eur. Respir. J.*, 3 (1990) 495–497.

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 (1989b) 706–710

Newman, S.P., Morén, F., Trofast, E., Talaee, N. and Clarke, S.W., Deposition and clinical efficacy of terbutaline sulphate from Turbuhaler, a new multi-dose powder inhaler. *Eur. Respir. J.*, 2 (1989a) 247–252.

Newman, S.P., Morén, F., Trofast, E., Talaee, N. and Clarke, S.W., Terbutaline sulphate Turbuhaler: effect of inhaled flow rate on drug deposition and efficacy. *Int. J. Pharm.*, 74 (1991) 209–213.

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

Pedersen, S., How to use a Rotahaler. *Arch. Dis. Childhood*, 61 (1986) 11–14.

Pedersen, S. and Steffersen, G., Fenoterol powder inhaler technique in children: influence of inspiratory flow rate and breath-holding. *Eur. J. Respir. Dis.*, 68 (1986) 207–214.

Pedersen, S., Hansen, O.R. and Fuglsang, G., Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch. Dis. Childhood*, 65 (1990) 308–310.

Siegel, S. and Castellan, N.J., *Non-parametric Statistics for the Behavioral Sciences*, McGraw-Hill, New York, 1988.

Smith, G., Hiller, C., Mazumder, M. and Bone, R., Aerodynamic size distribution of cromolyn sodium at ambient and airway humidity. *Am. Rev. Respir. Dis.*, 121 (1980) 513–517.

Vidgren, M.T., Vidgren, P.A. and Paronen, T.P., Comparison of physical and inhalation properties of spray-dried and mechanically micronised disodium cromoglycate. *Int. J. Pharm.*, 35 (1987) 139–144.

Vidgren, M.T., Karkkainen, A., Karjalainen, P., Paronen, P. and Nuutinen J., Effect of powder inhaler design on drug deposition in the respiratory tract. *Int. J. Pharm.*, 41 (1988) 211–216.

Zainudin, B.M.Z., Biddiscombe, M., Tolfree, S.E.J., Short, M. and Spiro, S.G., Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a metered dose inhaler, as a dry powder, and as a nebulised solution. *Thorax*, 45 (1990) 469–473.