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Total and regional lung deposition of terbutaline sulphate inhaled via a pressurised MDI or via Turbuhaler®

Lars Borgström [a] and Stephen Newman [b]

[a] *Human Pharmacology, Astra Draco AB, Box 34, 221 00 Lund (Sweden) and Dept of Biopharmaceutics and Pharmacokinetics, BMC, Box 580, 751 23 Uppsala (Sweden) and* [b] *Pharmaceutical Profiles, 2 Faraday Building, Highfields Science Park, University Boulevard, Nottingham NG7 2QP (UK)*

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Summary

The deposition patterns of terbutaline sulphate delivered from pressurized metered dose inhaler (MDI) and Turbuhaler® have been compared by gamma scintigraphy. The radionuclide ^{99m}Tc was used to label the formulations, and 1 mg terbutaline sulphate was subsequently inhaled from each device in a randomized cross-over fashion by eight healthy volunteers. Both devices were operated at their respective optimal inhalation flow rates. From the pressurised MDI, a mean 16.7% of the dose was deposited in the lungs (range 6.1–30.0%), compared to a mean 21.4% (range 14.1–30.8%) from Turbuhaler®. If the Turbuhaler® data were corrected for an observed mismatch in the size distributions of radiolabel and unlabelled drug, then the mean lung deposition from Turbuhaler® would be 29.3% of the dose. The distribution of radiolabel within the lungs was similar for each device, but oropharyngeal deposition was significantly reduced for Turbuhaler® ($P < 0.01$). It is concluded that pressurized MDI and Turbuhaler® produce broadly similar regional deposition in the lungs, but that the inter-subject variability of deposition is less for Turbuhaler®.

Introduction

Drugs used in the treatment of asthma, such as β_2-agonists, are most often administered via inhalation (Clark et al., 1991). The most common inhalation device is the metered dose inhaler, MDI (Morén, 1985), although more recently dry powder inhalers such as Rotahaler®, Diskhaler® and Turbuhaler® have been introduced to overcome the problems with coordination of the MDIs and as an alternative to the use of chlorofluorocarbon (CFC) propellants (Ganderton and Kassem, 1992). The quantity of drug deposited in the lungs, the effector site, is the major factor determining clinical efficacy of inhaled asthma medications (Mitchell et al., 1987); when the dose deposited in the lungs is increased, the elicited effect also increases until a maximal response is achieved (Ruffin et al., 1978). The degree of pulmonary deposition of inhaled drug is dependent not only upon the inhalation device used, but also on the drug substance and formulation

Correspondence to: L. Borgström, Human Pharmacology, Astra Draco AB, Box 34, 221 00 Lund, Sweden.

(Zainudin et al., 1990). Previous studies have suggested that only about 9% of the dose delivered from a terbutaline sulphate MDI is delivered to the lungs (Borgström and Nilsson, 1990), compared to, on average, twice this amount from the terbutaline sulphate Turbuhaler® (Newman et al., 1989a, 1991a; Borgström et al., 1993). However, no direct comparison of deposition patterns from these two devices has yet been made.

One advantage of topical drug administration is that therapeutic drug levels can be achieved in the effector organ without accompanying high systemic levels (Dolovich, 1989). Very small doses are needed to elicit the desired effects of β-agonists after inhalation (Ruffin et al., 1978), but if the delivery of inhaled drug could be directed to specific lung regions, even smaller doses of active substance might be needed. Thus, in addition to total lung deposition, the regional deposition of drug within the lungs might also be of interest. Scintigraphic measurements of deposition enable the amount of aerosol delivered into the lung to be assessed and also permit a ratio between peripheral and central deposition within the lungs to be determined (Agnew et al., 1982). In the present study we have compared by gamma scintigraphy in a group of healthy volunteers the total and regional depositions from both pressurised MDI and Turbuhaler® delivering terbutaline sulphate.

Materials and Methods

Subjects studied

Eight healthy volunteers (two men and six women) were included in the study. Their ages were between 19 and 28 years (mean 21 years), and all were non-smokers of at least 12 months duration. They were judged to be healthy by a physician after physical examination and laboratory tests. Their lung function tests were considered normal (the mean forced expiratory volume in one second (FEV_1) was 105% of predicted; range 92–119%). The design and study objectives were approved by the Quorn Research Review Committee, U.K., and the radioactive administrations by the Department of Health, U.K. The study was performed in accordance with the Declaration of Helsinki. Informed consent was given in writing.

Radiolabelling techniques

Terbutaline sulphate for use in Turbuhaler® and pressurised MDI was obtained from Astra Draco AB (Lund, Sweden) and was labelled with ^{99m}Tc on the actual study day at Pharmaceutical Profiles, Nottingham, U.K. The labelling of terbutaline sulphate for use in Turbuhaler® was performed in a manner similar to that previously described (Newman et al., 1989a). The radionuclide was extracted out of the aqueous phase in butanone (methyl ethyl ketone), which was then evaporated to dryness. Subsequently the radiolabel was re-dissolved in chloroform and was added dropwise to approx. 80 mg of spheronised terbutaline sulphate powder. Following complete evaporation of the chloroform, the labelled terbutaline sulphate powder was filled into an empty inhaler. Each metered dose from Turbuhaler® delivered approx. 5 MBq ^{99m}Tc plus 0.5 mg terbutaline sulphate. Labelling of terbutaline MDI was performed using a method previously described for labelling canisters containing either disodium cromoglycate (Newman et al., 1989b) or salbutamol (Newman et al., 1991b). Briefly, ^{99m}Tc was extracted out of the aqueous phase in butanone and after evaporation of the butanone in an empty MDI canister, the contents of a filled terbutaline sulphate canister containing drug, surfactant and propellants were added at below -60°C. A valve was attached by a crimper and the canister was vibrated in an ultrasonic shaker to disperse the radiolabel. Each metered dose from the MDI delivered approx. 2.5 MBq ^{99m}Tc plus 0.25 μg terbutaline sulphate in 25 μl propellant.

In order to determine the extent to which the distribution of radiolabel across different particle size fractions resembled that of the drug, measurements were performed with both pressurised MDI and Turbuhaler®, using a multistage liquid impinger operated at a flow rate of 60 l/min. The relative distributions of unlabelled drug, labelled drug and radiolabel in the impinger were assessed, as previously described (Newman et al., 1989a,b). The particle size ranges delivered to the

stages of the impinger were as follows: stage 1, > 10.5 μm; stage 2, 10.5–5.5 μm; stage 3, 5.5–3.3 μm; stage 4, < 3.3 μm. Particles penetrating beyond stage 2 (< 5.5 μm diameter) constitute the 'respirable fraction'.

Clinical procedures

Each volunteer was administered terbutaline sulphate tagged with ^{99m}Tc from pressurised MDI or Turbuhaler® upon two separate days at least 48 hours apart in a randomised cross-over fashion. In order to deposit approx. 10 MBq ^{99m}Tc in the body on each study day, four doses of terbutaline sulphate (total 1 mg) were given by pressurised MDI and two doses of terbutaline sulphate (total 1 mg) by Turbuhaler®. Administration of radioactive aerosol was performed with the inhaler connected in series with a Vitalograph MDI-Compact spirometer (Vitalograph Ltd, U.K.) modified for measuring inhalation flows. An average inhalation flow rate of 30 l/min was aimed at for the pressurised MDI and a peak inhalation flow rate of 60 l/min was aimed at for Turbuhaler®. These flow rates are believed to be optimal with respect to drug delivery to the lungs for the two devices (Newman et al., 1982; Pedersen et al., 1990). After inhalation the volunteers were instructed to hold their breath for 10 s before exhaling through an exhalation filter (Pall Ultipor, U.K.), that retains terbutaline inhaled into, but not deposited in, the lungs. The pressurised MDI was actuated by an investigator during the course of inhalation.

Lung function tests (FEV1, forced vital capacity (FVC) and peak expiratory flow rate (PEFR)) were measured by Vitalograph Spirometer immediately before inhalation of the labelled terbutaline, and then 15–30 min later, for a safety check to see that no deterioration in lung function had occurred.

Scintigraphy

Immediately after inhalation of study drug, a posterior view of the lungs, an anterior view of the lungs and a lateral view of the oropharynx were taken by gamma camera (General Electric Maxicamera) connected on line to a Nodecrest computer system. Gamma radiation from the mouthpiece and exhalation filter was also measured. All images were stored on magnetic tape for subsequent data analysis. From these measurements the metered dose could be fractionated into that (1) in the lungs, (2) in the oropharynx, (3) in the mouthpiece, and (4) in the exhaled air.

On one of the study days, a posterior lung ventilation scan was performed using the radioactive inert gas ^{81m}Kr. Regions of interest were drawn around central (C), intermediate, and peripheral (P) lung zones, which were subsequently superimposed upon the aerosol views enabling the percentage of the aerosol dose in each of these zones to be determined. The regions were defined as previously described (Agnew et al., 1982; Newman et al., 1989a,b), and the peripheral zone/central zone deposition ratio (P/C ratio) was calculated.

Statistical tests

Statistical comparisons were performed using paired Student's t-test. A P value of < 0.05 was considered significant.

Results

Particle size distributions of unlabelled drug, labelled drug and radiolabel as assayed with the multistage liquid impinger are given in Fig. 1. Particles from stages 3 and 4, and the filter, make up the respirable fraction (< approx. 5.5 μm diameter). For MDI this fraction was 34.5, 34.3, and 37.4% for unlabelled drug, labelled drug and radiolabel, respectively. For Turbuhaler® the corresponding values were 31.7, 26.7, and 23.2%. The ratio for the fraction of respirable particles for unlabelled drug/radiolabel thus was 0.92 for MDI and 1.37 for Turbuhaler®.

The average inhalation flow rates from the pressurised MDI, and the peak inhalation flow rates from the Turbuhaler®, together with inhaled volumes and breath holding times are given in Table 1. The desired average flow rate for MDI was 30 l/min and the mean observed value was 33.8 l/min (the range for individual breaths was 22.9–48.6 l/min). For Turbuhaler® the de-

TABLE 1

Inhalation details for MDI and Turbuhaler study days

Subject	MDI			Turbuhaler		
	Flow rate (l/min)	Inh. Vol. (l)	BHT (s)	Flow rate (l/min)	Inh. Vol. (l)	BHT (s)
1	29.6	2.73	8.7	57.0	2.81	8.8
2	27.2	2.22	10.6	52.5	1.93	10.1
3	39.9	2.17	9.1	61.0	2.63	8.5
4	23.5	1.96	8.7	48.5	1.44	9.5
5	34.5	2.59	8.6	57.5	1.61	10.1
6	34.0	2.95	9.0	57.0	2.51	9.5
7	37.9	3.87	8.4	66.0	3.81	9.3
8	43.4	4.42	9.4	62.5	3.60	9.1
Mean	33.8	2.86	9.1	57.8	2.54	9.4
SD	6.7	0.87	0.7	5.6	0.87	0.6

Values for MDI are mean of four doses and for Turbuhaler of two doses. BHT, breath holding time.

sired peak flow rate was 60 l/min and the mean observed value was 57.8 l/min (range for individual breaths 48.5–66.0 l/min). These data showed that the technical performance of the inhalations was good, and that the inhalation parameters achieved were close to targeted values.

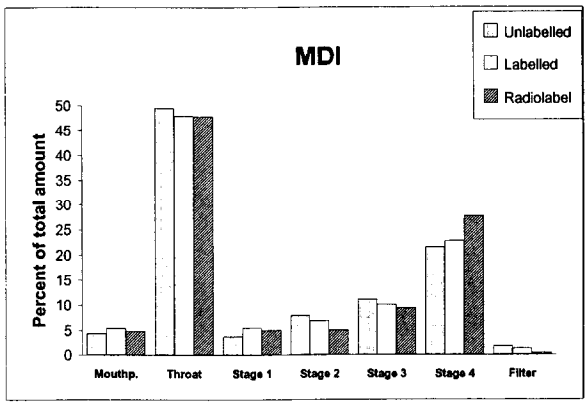
Results on pulmonary deposition, as well as retention in mouthpiece and exhalation filter, are given in Tables 2 and 3. Total lung deposition was 16.7% of the dose (coefficient of variation (CV) = 57%) for pressurised MDI and 21.4% of the dose (CV = 29%) for Turbuhaler®. The difference was not significant ($P = 0.314$) although six of the eight subjects had a higher lung deposition with Turbuhaler® than with pressurised MDI. Oropharyngeal deposition averaged 68.3 and 47.2% of the dose for MDI and Turbuhaler®, respectively ($P < 0.01$), and actuator or mouthpiece retention averaged 13.4 and 30.0%. respectively ($P < 0.01$). The distribution within the lungs was similar for pressurised MDI and Turbuhaler®. The ratio between peripheral and central deposition (P/C) was 1.71 (range 1.20–2.54) for MDI and 1.62 (range 1.03–2.14) for

TABLE 2

Deposition of radioactive drug after inhaling via MDI

Subject	Actuator	Oropharynx	Total lung	Regional lung			P/C ratio	Exhaled
				Central	Intermed.	Peripheral		
1	15.5	76.3	7.1	1.7	2.4	3.1	1.87	1.1
2	10.4	81.8	6.1	1.2	1.9	3.0	2.54	1.6
3	15.6	66.2	12.5	2.9	4.3	5.4	1.86	5.8
4	12.8	75.6	10.9	3.2	3.9	3.8	1.20	0.8
5	11.7	66.3	21.8	6.5	7.1	8.2	1.27	0.2
6	11.8	57.6	30.0	7.8	9.3	12.9	1.65	0.6
7	13.1	71.7	15.0	4.1	5.5	5.4	1.31	0.3
8	16.0	51.0	30.0	6.3	11.2	12.6	2.00	3.0
Mean	13.4	68.3	16.7	4.2	5.7	6.8	1.71	1.7
SD	2.1	10.2	9.6	2.4	3.3	4.0	0.45	1.9

Values are given in % of metered dose. P/C ratio is the ratio between peripheral and central deposition.



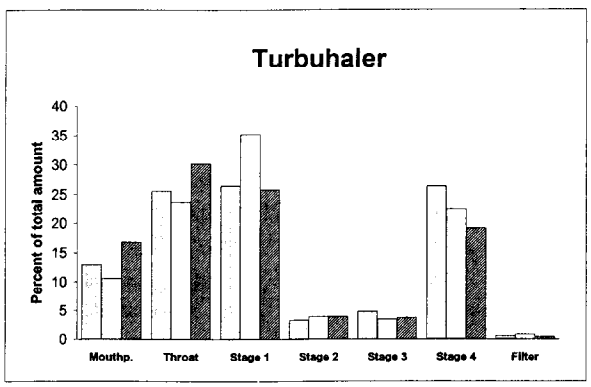


Fig. 1. Percentage of unlabelled drug, labelled drug and radiolabel from pressurized MDI and from Turbuhaler® within the mouthpiece, throat, four stages and final filter of a multistage liquid impinger.

Turbuhaler®, respectively. Radioactivity in exhaled air was less than 2% for both devices.

Discussion

The present study is the first to utilise direct gamma-labelling of a terbutaline sulphate formulation in a pressurised MDI. Previous studies using the same aerosol canisters have used ^{99m}Tc-labelled Teflon particles as a replacement for the drug particles. These studies, when performed under inhalation conditions similar to those in the present study, resulted in a mean 14% of the dose deposited in the lungs in a group of asthmatic patients (Newman et al., 1982). In a later study, using activated charcoal to block the oral uptake of terbutaline, 9% of the delivered dose was deposited in the lungs of a group of healthy volunteers, using a peak inhalation flow rate of 86 l/min (Borgström and Nilsson, 1990).

For Turbuhaler® a number of studies with ^{99m}Tc-labelled terbutaline sulphate have been performed with mean lung deposition values ranging from 14 to 27% (Newman et al., 1989a, 1991a; Borgström et al., 1992, 1993). The present result, mean 21%, fits well within this range. The degree of retention in the mouthpiece (approx.

TABLE 3

Deposition of radioactive drug after inhaling via Turbuhaler

Subject	Mouthpiece	Oropharynx	Total lung	Regional lung			*P/C* ratio	Exhaled
				Central	Intermed.	Peripheral		
1	34.1	39.7	24.3	6.6	8.3	9.5	1.44	1.9
2	26.6	42.8	27.8	6.3	8.3	13.1	2.07	2.8
3	24.5	50.9	22.9	4.9	7.5	10.5	2.14	1.8
4	20.8	61.3	16.9	4.5	5.4	7.0	1.55	1.1
5	42.4	41.7	15.1	4.5	4.8	5.9	1.30	0.8
6	29.3	39.0	30.8	8.0	10.5	12.3	1.53	0.9
7	16.4	63.7	19.1	5.9	7.0	6.1	1.03	0.8
8	46.1	38.8	14.1	3.2	4.9	6.1	1.92	0.9
Mean	30.0	47.2	21.4	5.5	7.1	8.8	1.62	1.4
SD	10.3	10.2	6.1	1.5	2.0	2.9	0.39	0.7

Values are given in % of metered dose. *P/C* ratio is the ratio between peripheral and central deposition.

30% of the dose) was, however, higher than that observed previously and oropharyngeal deposition consequently lower. For studies with both pressurised MDI and Turbuhaler®, the inhalations were performed in the desired manner, and the represented 'optimal' inhalation technique for each device (Newman et al., 1982; Pedersen et al., 1990).

Radiolabelling of an inhaled formulation involves a risk of modifying the formulation properties that could in turn affect particle size distribution in the aerosol cloud. This could manifest itself as a mismatch between the distributions of unlabelled drug, labelled drug and radiolabel, as measured by multistage liquid impinger. For the pressurised MDI, these distributions were similar (ratio of respirable unlabelled drug to respirable radiolabel 0.92), but for Turbuhaler® the agreement was less good (ratio of respirable unlabelled drug to respirable radiolabel 1.37). A similar degree of mismatch for terbutaline sulphate Turbuhaler® was observed in an earlier study (Newman et al., 1989a). This may result from the effects on the drug particles of impurities in the chloroform used as a vehicle for the radiolabel, although we attempted to overcome this potential problem by using HPLC grade chloroform. This mismatch suggests that the use of the radiolabel as a marker for unlabelled drug underestimates deposition in the lung from Turbuhaler® in this study, and that a more correct lung deposition value after inhaling via Turbuhaler® can be obtained by multiplying the measured mean deposition (21.4% of the dose) by the calculated ratio 1.37. This gives a mean value of 29.3% of the dose as a corrected lung deposition figure. Further, it is likely that this revised deposition estimate for Turbuhaler® would result in significantly greater lung deposition than that from the pressurised MDI.

Regional deposition can be expressed as the ratio between peripheral and central deposition, ie the P/C ratio. This ratio for the MDI formulation was 1.71 and for Turbuhaler® 1.62, and the difference was not significant. The value for Turbuhaler® was lower than has been observed in previous studies involving healthy volunteers (Borgström et al., 1993) where values of about 2.3 were obtained. In our two previous studies (Borgström et al., 1992, 1993) the regional deposition was 5.7, 8.4, 12.9% and 6.4, 8.5, 12.1% for the central, intermediate, and peripheral regions, respectively. The difference between those studies and the present study is the degree of deposition in the peripheral region, which in the present study was 8.8%. This reduction in the delivery to peripheral lung could be a consequence of the mismatch between the drug and radiolabel distributions.

The lung deposition for pressurised MDI had a 4.9-fold spread of values (6.1 30.0% of the dose), compared to a 2.2-fold spread of values (14.1–30.8% of the dose) for Turbuhaler®. This lower inter-subject variability of deposition from Turbuhaler® is to be expected on theoretical grounds, since deposition is dominated less by inertial impaction in the oropharynx than that from the pressurised MDI. Impaction is highly dependent upon inter-individual differences in anatomy and local air-flow patterns (Gerrity, 1990). This lower variability of deposition from Turbuhaler® is of particular interest, since there is concern that powder inhalers show greater variability between delivered doses. Our data suggest that in vivo Turbuhaler® is the more reproducible drug delivery device.

In conclusion, we have shown that the regional lung deposition was similar for terbutaline sulphate MDI and Turbuhaler®. Total lung deposition for Turbuhaler® averaged higher than for MDI.

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