

## Deposition and clinical efficacy of terbutaline sulphate from Turbuhaler, a new multi-dose powder inhaler

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*Deposition and clinical efficacy of terbutaline sulphate from Turbuhaler, a new multi-dose powder inhaler. S.P. Newman, F. Morén, E. Trofast, N. Talae, S.W. Clarke.*

**ABSTRACT:** A radioaerosol technique has been developed in order to assess deposition patterns from a new metered dose powder inhaler (Turbuhaler, Astra Pharmaceuticals). The radionuclide  $Tc^{99m}$  dissolved in chloroform was added to a spheronised formulation of micronised terbutaline sulphate and the chloroform was allowed to evaporate. Turbuhaler subsequently delivered 0.5 mg of treated drug per metered dose. *In vitro* tests with a multistage liquid impinger showed that the fractionation of the drug dose between different particle size bands was similar to the fractionation of radioactivity. In a group of ten asthmatic patients, a mean 14.2% (SEM 2.1) of the drug dose was deposited in the lungs, with 71.6% (3.0) of the dose in the oropharynx. Of the remainder, 13.7% (2.1) was deposited on the mouthpiece, and 0.5% (0.2) recovered from exhaled air. The radiolabel was present in both central and peripheral zones of the lungs. All patients bronchodilated; forced expiratory volume in one second ( $FEV_1$ ) increased from 1.40 (0.24) l to 1.77 (0.24) l ( $p < 0.01$ ) 20 min after inhalation. These results suggest that both the distribution of drug and the clinical effect of terbutaline sulphate delivered from Turbuhaler are similar to those from a pressurised metered dose inhaler (MDI).

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Many patients unable to use a pressurised metered dose inhaler (MDI) correctly can benefit from a breath-actuated dry powder device since it is not necessary for the patient to coordinate inhalation with actuation [1-3]. These devices are inconvenient, however, because in previously available models a capsule containing the drug powder must be loaded into the inhaler prior to use. These capsules may be difficult for patients to load in acute situations, and furthermore, the capsules may occasionally fail to break or may empty incompletely [4, 5]. A new multidose powder inhaler (Turbuhaler, AB Draco (subsidiary to AB Astra)) has thus been designed for delivery of the bronchodilator terbutaline sulphate. Turbuhaler (fig. 1) contains 200 metered doses of 0.5 mg terbutaline sulphate, each dose being loaded into a dosing unit prior to inhalation by a simple turning mechanism. The drug is dispersed into the inhaled airstream by the patient's inspiratory effort.

Although deposition patterns in the lungs and oropharynx from both MDIs [6-8] and nebulisers [9, 10], have been widely assessed, little comparable data exist for dry powder inhalers. Pharmacokinetic studies [11] have suggested that no more than 10% of the dose reaches the lungs from one type of powder inhaler. Aerosol deposition and clinical efficacy of terbutaline sulphate have thus been assessed simultaneously for Turbuhaler in a group of asthmatic patients.

### Patients and methods

#### *Radiotracer technique*

A new radiotracer method has been developed, involving the addition of the radionuclide  $Tc^{99m}$  (physical half-life 6 h, gamma ray energy 140 KeV) to the bronchodilator terbutaline sulphate in such a manner that the radionuclide was associated with the drug particles at the time of inhalation. The radionuclide was eluted from a generator (Amersham International) and 1.5 ml of the eluate was placed in a small shielded glass test tube. The radionuclide was then extracted out of the aqueous phase in chloroform according to the technique originally described by Few *et al.* [12] for the preparation of labelled polystyrene spheres. One drop of ammonia and one drop of tetraphenylarsonium chloride (TPAC, 5% aqueous solution) were added to the eluate. Chloroform (1.5 ml) was then added and the test tube shaken in an ultrasonic vibrator for 5 s before filtering through a silicone-treated phase-separating filter paper (Whatman). The filtrate contained approximately half the original activity in the form of tetraphenylarsonium pertechnetate dissolved in chloroform; this was added subsequently by hypodermic syringe to 50 mg micronised terbutaline sulphate, aggregated as spheres of diameter less than 1 mm, in a small glass beaker at 70°C. Evaporation of



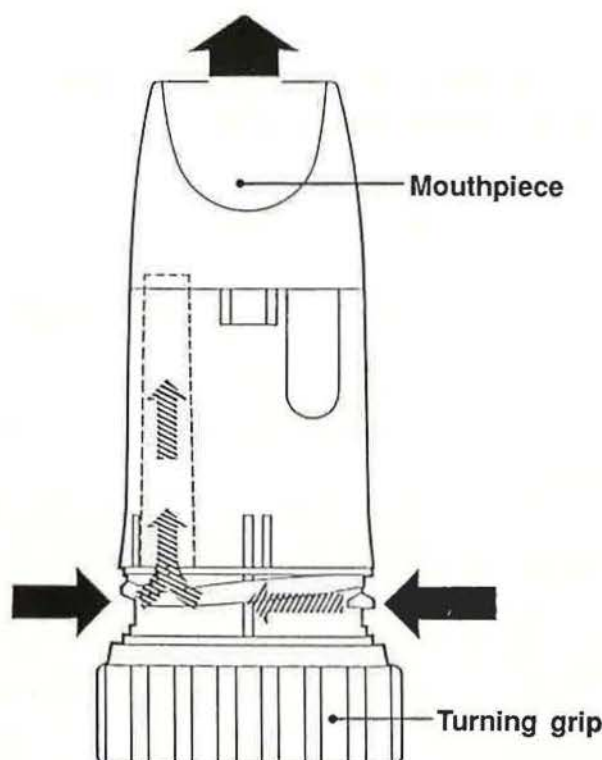


Fig. 1. — Diagram of the Turbuhaler. A metered dose is loaded into a dosing unit by turning the base of the device; inhaled air passes through the device and disperses the drug powder.

chloroform was virtually instantaneous, and the dry terbutaline sulphate was filled into an empty inhaler. A mouthpiece was added, and the inhaler was primed by extracting 10 doses *via* a filter at 60 l·min<sup>-1</sup> using a backing pump.

A multistage liquid impinger [3] was used to examine the quantities of drug and radiolabel in different particle size fractions, and hence the extent to which the distribution of radiolabel reflected that of the drug. The impinger comprised four impaction stages to trap particles of different sizes, a 90° bend or throat prior to the first impaction stage and a low resistance bi-directional filter (Inspiron 002290) beyond the fourth stage to trap any very fine particles. The air flow rate through the impinger was set at 60 l·min<sup>-1</sup> with Turbuhaler inserted at the entrance to the throat. The approximate size bands trapped on the 4 stages were: stage 1, 10 to 25 µm; stage 2, 5.5 to 10 µm; stage 3, 3.3 to 5.5 µm; stage 4, 0.8 to 3.3 µm. Ten doses were drawn into the impinger from an inhaler filled with the chloroform-treated terbutaline sulphate, and the mouthpiece, throat and four impaction stages were washed out with 50 ml distilled water. The terbutaline sulphate content of each of these samples was assessed by an ultraviolet spectrophotometer (Pye Unicam SP 1800) operating at a wavelength of 280 nm. Radioactivity in each 50 ml sample was measured with two diametrically opposed scintillation probes. Five individual inhalers were assessed in this manner. Tests were also performed on inhalers filled with terbutaline sulphate which had not been treated with chloroform, in

order to assess whether the presence of chloroform changed the particle size distribution.

#### Studies in patients

Radioaerosol studies were performed on 10 patients with reversible airways obstruction (six males, four females, age range 21–76 yrs, baseline forced expiratory volume in one second (FEV<sub>1</sub>) 25–100 % predicted); each patient had shown previously an increase in FEV<sub>1</sub> greater than 20% following bronchodilator inhalation from a metered dose inhaler. Patients gave informed consent in writing to taking part in the studies. Approval was obtained from both the Ethical Practices Sub-Committee of the Royal Free Hospital and the Administration of Radioactive Substances Advisory Committee.

On arrival at the Laboratory, patients first performed lung function tests (FEV<sub>1</sub> by Vitalograph spirometer, peak expiratory flow rate (PEFR) by Wright peak flow meter and maximum expiratory flow rate at 75% of forced vital capacity ( $\dot{V}_{max25}$ ) by Ohio Spirometer coupled to an X-Y plotter), having withheld the use of inhaled bronchodilators for at least 12 h. After practising with a dummy inhaler, a single metered dose was delivered from an inhaler to which 50 mg terbutaline sulphate plus 370 MBq (10 mCi) Tc<sup>99m</sup> had been added. Each metered dose delivered approximately 3.7 MBq (100 µCi) Tc<sup>99m</sup>. Turbuhaler was partially shielded during the inhalation manoeuvre by a small lead sleeve which did not impede the working parts of the inhaler. Patients were instructed to exhale, place the mouthpiece between the lips, inhale deeply and rapidly (approximately 60 l·min<sup>-1</sup>), breath-hold for approximately 10 s, and then exhale *via* a low resistance filter (Inspiron 002290) to trap any exhaled aerosol. Inhalations were monitored by respiratory inductive plethysmography (Respirace Corporation) with inductance bands worn around the chest and abdomen as described previously [13]. A General Electric 400 T large-field-of-view gamma camera was used immediately after inhalation to obtain a posterior-anterior view of the chest and stomach (minimum 20,000 counts) and a lateral view of the oropharynx (minimum 10000 counts). Scanning was complete within 3 min of inhalation. In order to relate the distribution of radioaerosol to the dimensions of the lung, patients then inhaled Kr<sup>81m</sup> gas from a generator (MRC Cyclotron Unit, Royal Postgraduate Medical School, London) and a further posterior-anterior view of the lungs was obtained. Measurements of FEV<sub>1</sub>, PEFR and  $\dot{V}_{max25}$  were repeated 20 min after inhalation.

Quantities of aerosol present in the mouthpiece and exhalation filter were determined by comparison with a calibration dose drawn from Turbuhaler into a second filter by a backing pump. The remainder of the dose was assumed to be in the patient and was divided into amounts initially deposited in lungs and oropharynx according to the counts in computer-generated regions of interest. Count rates were corrected for gamma ray absorption in the chest and oropharynx. The distribution of activity within the lungs was determined from three further regions of interest comprising central, intermediate and



peripheral lung zones (fig. 2). The 20% contour of the  $Kr^{81m}$  ventilation scan was used to define the lung edges and activities in the different regions were summed for right and left lungs.

## Results

### Evaluation of radiotracer technique

Amounts of untreated and chloroform-treated drug recovered from mouthpiece, throat and impaction stages are shown in table 1, expressed as fractions of 0.5 mg dose. For the untreated drug, a mean 178 (SEM 14)  $\mu$ g was contained in stages 3 and 4 of the impinger, compared with 144 (9)  $\mu$ g of the treated drug. More drug was recovered from stage 1 with the treated drug. Table 1 also shows the amounts of drug represented by the radioactivity recovered from different parts of the impinger system; the distribution of radioactivity among different particle size fractions was virtually identical to that of the treated drug. Radioactivity equivalent to 137 (7)  $\mu$ g terbutaline sulphate was recovered from stages 3 and 4. The treated and untreated drug dissolved at similar rates in water, and it was concluded that the addition of chloroform, ammonia and TPAC did not alter water-solubility.

Table 1. — Mean recovery of drug ( $\mu$ g, with SEM in parenthesis,  $n=5$ ) from inhaler mouthpiece and from impinger, after administration of a 500  $\mu$ g dose. Ten metered doses were collected from each inhaler

	Untreated drug	Chloroform - treated drug	Drug represented by radioactive count rates
Mouthpiece	68 (8)	52 (3)	50 (3)
Throat	59 (8)	51 (6)	48 (7)
Stage 1	162 (20)	221 (17)	233 (16)
Stage 2	33 (4)	32 (2)	32 (2)
Stage 3	30 (2)	20 (1)	20 (1)
Stage 4	148 (12)	124 (9)	117 (7)

### Patient studies

A typical deposition pattern in one patient is shown in fig. 2. The major site of deposition was in the oropharynx, some of the deposited material having been swallowed, and only the minority of the dose was in the lungs. Quantification of the scans in the group of 10 patients (table 2) showed that a mean 14.2 % (SEM 2.1) of the dose was deposited in the lungs and 71.6 % (3.0) in the oropharynx. The remainder of the dose was either retained on the mouthpiece or exhaled. The central lung zone contained 5.6 % (0.8), the intermediate zone 3.3 % (0.5) and the peripheral zone 5.3 % (1.2) of the dose.

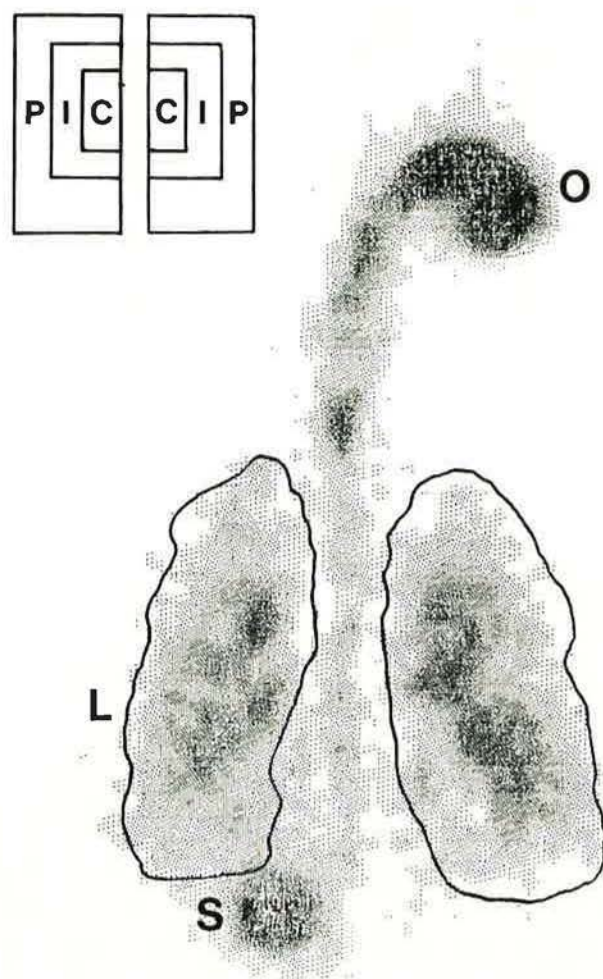


Fig. 2. — Typical deposition pattern in one patient with asthma. L: lungs; O: oropharynx; S: stomach. The view is posterior – anterior. The 20% contour of a  $Kr^{81m}$  ventilation scan is superimposed on the aerosol view. The inset shows the division of the lungs into central (C), intermediate (I) and peripheral (P) zones.

Changes in lung function 20 min post-inhalation are shown in fig. 3.  $FEV_1$  increased from 1.40 (0.24) l to 1.77 (0.24) l ( $p<0.01$ , Wilcoxon Rank-Sum Test),  $PEFR$  from 228 (40)  $l \cdot min^{-1}$  to 294 (38)  $l \cdot min^{-1}$  ( $p<0.01$ ) and  $\dot{V}_{max25}$  from 0.27 (0.05)  $l \cdot s^{-1}$  to 0.62 (0.12)  $l \cdot s^{-1}$  ( $p<0.01$ ).

The inhalation manoeuvre was assessed fully in eight of the 10 patients, the respiratory inductive plethysmography traces being inadequate in the remaining two patients. The mean inhaled flow rate through Turbuhaler was 56  $l \cdot min^{-1}$  (range 45–70  $l \cdot min^{-1}$ ) and the mean inhaled volume 2.00 l (range 0.70–4.60 l). There was no significant correlation between inhaled flow rate and percentage predicted  $FEV_1$  (Spearman rank correlation test). Within the patient group, total lung deposition, peripheral lung deposition and the peripheral zone/central zone ratio did not correlate with either inhaled flow rate or percentage predicted  $FEV_1$ , but the peripheral zone/central zone ratio was significantly correlated with inhaled volume ( $r=0.74$ ,  $p=0.05$ ).



Table 2. — Fractionation of the terbutaline sulphate dose in patients; FEV<sub>1</sub> values and inhaled flow rates

Patient number	FEV <sub>1</sub> % predicted	Inhaled flow rate l·min <sup>-1</sup>	Percentage of dose deposited in:			
			Lungs	Oropharynx	Mouthpiece	Exhaled
1	49	46	20.8	50.4	27.8	1.0
2	28	50	8.6	82.3	7.6	1.5
3	30	55	13.9	75.4	10.5	0.2
4	56	-	18.5	77.2	4.2	0.1
5	43	45	10.1	71.9	17.8	0.2
6	32	-	10.2	74.3	15.5	0.1
7	78	61	18.4	69.8	11.4	0.3
8	40	70	26.8	60.4	12.1	0.7
9	100	64	4.9	76.1	18.6	0.4
10	25	59	9.4	78.3	11.8	0.4
Mean	48	56	14.2	71.6	13.7	0.5
SEM	4	3	2.1	3.0	2.1	0.2

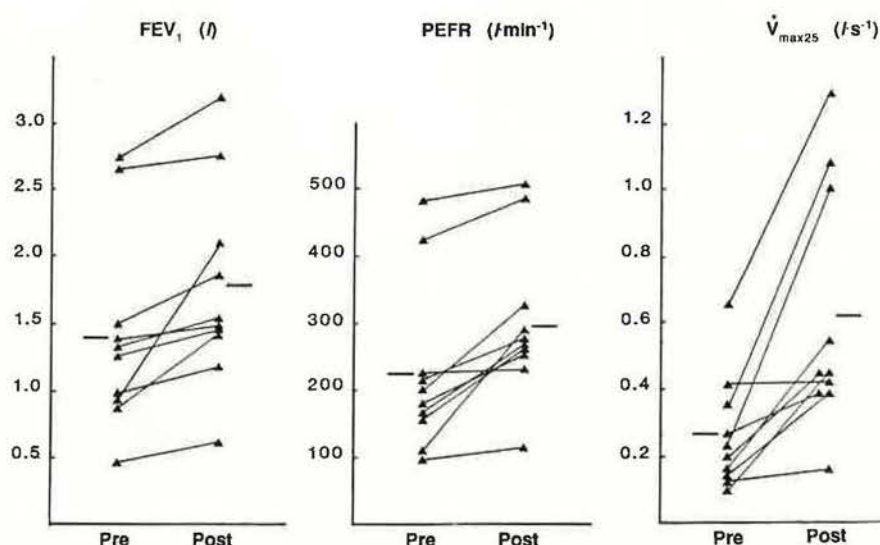


Fig. 3. — FEV<sub>1</sub>, PEFR and  $\dot{V}_{\max 25}$  pre-inhalation and 20 min post-inhalation of 0.5 mg terbutaline sulphate from Turbuhaler in 10 asthmatic patients. The horizontal bars show mean values pre- and post-inhalation. FEV<sub>1</sub>: forced expiratory volume in one second; PEFR: peak expiratory flow rate;  $\dot{V}_{\max 25}$ : maximum expiratory flow rate at 75% vital capacity.

### Discussion

Earlier studies designed to assess drug delivery from powder inhalers have used drugs labelled with the beta ray emitting radionuclides H<sup>3</sup> and C<sup>14</sup> which cannot be measured by an external radiation detector [11]. The radionuclide Tc<sup>99m</sup> has not been chemically labelled to terbutaline sulphate in the present study, but was added to the drug spheres in a volatile solvent. These spheres de-aggregate in the inhaler mouthpiece, partly by turbulence and partly by a direct mechanical effect. Deposition studies in a group of asthmatic patients showed that only a small percentage of the dose reaches the lungs. This percentage is similar to that reaching the lungs from a pressurised MDI which has been estimated variously as <10% of the dose [11], 13–29% of the dose [8], 7–25% of the dose [6, 14] up to 13.6% of the dose [7] and 10 to 40% of total deposition in the body [15]. Deposition in the oropharynx and mouthpiece, and recovery from exhaled air were also similar to those observed for MDIs. Very recently, VIDGREN *et al.* [16] measured deposition

from various powder inhalers using spray-dried particles of sodium cromoglycate labelled with Tc<sup>99m</sup>; they found 6–16% of the dose in the lungs and 31–59% in the oropharynx.

Although it was not possible in the present study to assess the precise distribution of the drug between large airways, small airways and alveoli, analysis of the scans showed aerosol to be present in central, intermediate and peripheral lung zones. We did not observe a significant correlation between regional distribution and the degree of airway obstruction; such a correlation occurs with monodisperse test aerosols inhaled under steady breathing conditions [17], but studies of pressurised aerosol deposition have shown similar regional deposition patterns in normal subjects and in patients with obstructive airways disease [18, 19].

When the radiotracer method was evaluated *in vitro*, there was almost perfect agreement between the distribution of treated drug and radiolabel on the various parts of the multistage liquid impinger. Hence the amounts of radioactivity detected in lungs and oropharynx should



accurately reflect the amounts of treated drug delivered to these sites. However, the addition of chloroform to the drug spheres produced a small change in the particle size distribution, with more large particles trapped on stage 1 of the impinger and fewer small particles trapped on stage 4. This suggests that deposition in the lungs may have been underestimated in this study; a correction could be applied by multiplying the measured lung deposition figures by the ratio of untreated drug in particles less than 5.5  $\mu\text{m}$  diameter to drug represented by radioactivity in particles less than 5.5  $\mu\text{m}$  diameter, i.e. 178  $\mu\text{g}$  / 137  $\mu\text{g}$  or 1.30. The percentage of the aerosol dose detected in the lungs was smaller than that penetrating to stages 3 and 4 of the impinger, probably reflecting the difficulty that aerosol particles experience in penetrating the oropharynx at relatively high inhaled flow rates, and the designation of these particles as "respirable" can only be approximate.

Patients were instructed to inhale rapidly in this study in order to enhance the de-aggregation of the drug spheres and to ensure an adequate quantity of respirable aerosol [3]. The standardisation of the inhaled flow rate to a narrow range may explain why we were unable to show a relationship between inhaled flow rate and deposition patterns. However, recent studies in children [5, 20] and in adults [21] have shown that inhaling rapidly through Rotahaler (Allen and Hanburys) and Berotec Inhaler (Boehringer Ingelheim) is more effective than inhaling slowly. For the Spinhaler (Fisons) rapid inhalation increases the quantities of sodium cromoglycate found in blood and urine following absorption via the lungs [22]. This is in contrast to the pressurised MDI where slow inhalation should be adopted [23]. The technique presented in this study lends itself to the evaluation of different inhalation techniques through Turbuhaler, in terms of both lung deposition and clinical responses, and also to assessment of drug delivery from other dry powder systems.

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*Dépôt et efficacité clinique du sulfate de terbutaline administré par le Turbuhaler, un nouvel inhalateur de poudre à dose multiple. S.P. Newman, F. Morén, E. Trofast, N. Talaee, S.W. Clarke.*

RÉSUMÉ: Nous avons développé une technique de radio-aérosol pour apprécier les types de dépôt de médicaments provenant d'un nouvel inhalateur doseur de poudre (Turbuhaler, Astra Pharmaceuticals). L'isotope  $\text{Tc}^{99\text{m}}$  a été dissous dans le chloroforme et additionné à une formulation sphéronisée de sulfate de terbutaline micronisé; l'on a laissé le chloroforme s'évaporer. Le Turbuhaler a été ensuite utilisé pour donner 0.5 mg du médicament par dose mesurée. Les tests in vitro avec un impacteur liquide à stade multiple ont montré que le fractionnement de la dose de médicament dans les différentes bandes de taille particulaire était similaire au fractionnement de la

radio-activité. Dans un groupe de dix patients asthmatiques, une moyenne de 14.2 (SEM 2.1) % du médicament se dépose dans les poumons, alors que 71.6 (3.0) % de la dose vont dans l'oropharynx. Du solde, 13.7 (2.1) % se déposent dans la pièce buccale et 0.5 (0.2) % est récupéré dans l'air expiré. Le marqueur radio-actif était présent à la fois dans les zones centrales et périphériques des poumons. Tous les patients ont obtenu une

bronchodilation; le VEMS a augmenté de 1.40 (0.24) l à 1.77 (0.24) l ( $p < 0.01$ ) 20 minutes après l'inhalation. Ces résultats suggèrent que la distribution de la drogue et l'effet clinique du sulfate de terbutaline dispensé à partir du Turbuhaler sont semblables à ceux obtenus à partir d'un aérosol doseur standard.

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