Comparison of Gamma Scintigraphy and a Pharmacokinetic Technique for Assessing Pulmonary Deposition of Terbutaline Sulphate Delivered by Pressurized Metered Dose Inhaler

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A comparison has been made of pulmonary deposition of terbutaline sulphate from a pressurized metered dose inhaler (pMDI), measured in 8 healthy male subjects by gamma scintigraphy and by a pharmacokinetic (charcoal-block) method, involving drug recovery in urine. Measurements were carried out with a pMDI at slow (27 l/min) and fast (151 l/min) inhaled flows and with Nebuhaler® large volume spacer device (average inhaled flow 17 l/min). Overall, the two methods did not differ significantly in their estimates of whole lung deposition, although values obtained by gamma scintigraphy exceeded those from the charcoal-block method for the pMDI with fast inhalation. The regional distribution of drug within the lungs and deposition in the oropharynx could be assessed by gamma scintigraphy, but not by the charcoal-block method. It is concluded that either method may be used to assess whole lung deposition of terbutaline sulphate from pMDIs, both with and without a spacer, although each method has its own inherent advantages and disadvantages.

KEY WORDS: aerosol; terbutaline sulphate; gamma scintigraphy; charcoal-block; lung deposition.

INTRODUCTION

The pulmonary deposition of inhaled drugs may be studied by gamma scintigraphy, in which the drug formulation is radiolabelled by an appropriate gamma-ray-emitting radionuclide and its deposition monitored *in-vivo* by a gamma camera (1, 2). Gamma-scintigraphy has been applied widely to the assessment of drug delivery from nebulizers, pressurized metered dose inhalers (pMDIs) and dry powder inhalers (2). Drug delivery may also be assessed by pharmacokinetic methods. Following inhalation, a bronchodilator drug can reach the systemic circulation as a result of absorption *via* the lungs and the gastrointestinal tract. If the buccal and gastrointestinal uptake of oropharyngeally deposited drug is blocked with activated charcoal (3, 4), then the amount of intact drug excreted into the urine compared with the urinary excretion of an intravenous reference dose will be a measure of the amount of drug absorbed *via* the lungs, assuming that the drug is not metabolized in the lungs. To date, this technique (the charcoal-block method) has been validated for the bronchodilator terbutaline sulphate (4) and for the topical corticosteroid budesonide (5). In a previous study involving a multidose dry powder inhaler (Turbuhaler®) a slightly higher mean value for lung deposition in 6 healthy volunteers was obtained by gamma scintigraphy than by the charcoal-block method (6). The objective of the present study was to obtain further comparative data between the two methods for terbutaline sulphate delivered by pMDI using three different delivery techniques.

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MATERIALS AND METHODS

Subjects

Eight healthy male non-smoking volunteers (age range 20 to 45 years; forced expiratory volume in one second 88 to 120% predicted) took part in an open and randomised three period cross-over study to assess the deposition of terbutaline sulphate from pMDIs. Each subject underwent a medical examination pre-study within 21 days of the first study day, and post-study within 14 days of the last study day. Subjects with a history of chronic respiratory disease, or who had recent symptoms of an upper or lower respiratory tract infection were excluded. Following perusal of an information sheet describing the study, each subject was asked to give written informed consent in the presence of a witness. The study was approved by the Quorn Research Review Committee, and permission to administer the radionuclide for the scintigraphic measurements was obtained from the Department of Health, UK.

Radiolabelled pMDIs

Inhalers delivering 250 μg terbutaline sulphate per metered dose (Astra Pharmaceuticals) were radiolabelled by the addition of the radionuclide ^{99m}Tc, as previously described (7, 8, 9) and delivered 5 MBq ^{99m}Tc, in addition to the drug substance, in each metered dose. The inhalers used on the study days were analysed by multistage liquid impinger operated at a flow of 60 l/min (10) in order to ascertain that the distribution of the radiolabel in different particle size fractions matched that of the drug substance. The particle size distributions of terbutaline sulphate from canisters that had not been radiolabelled were also measured. The amount of drug per metered dose from the canisters used on the study days was assessed.

Drug inhalation

The volunteers were each studied on three occasions at least 72 hours apart with subjects instructed to inhale at specific average flows on each study day. A total of 500 μg (2 doses) terbutaline sulphate was delivered by: (a) pMDI (targeted average inhaled flow 30 l/min), (b) pMDI (targeted average inhaled flow 180 l/min), or (c) pMDI plus Nebuhaler® 750 ml spacer device (Astra Pharmaceuticals, targeted average inhaled flow 15 l/min). Subjects were asked to target their flows to the required values by following a set of cursors on the screen of a Vitalograph pMDI-Compact spirometer (Vitalograph, Buckingham, UK) connected in series with the inhalers. The pMDIs were fired by an observer; for the conventional pMDI the inhaler was fired during inhalation, while for the Nebuhaler® the inhaler was fired 5 seconds

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before inhalation commenced. After inhalation, breath was held for 10 seconds, and the subject then exhaled *via* a filter. In order to ensure complete emptying of the spacer, a second breath was taken after each dose, again followed by 10 seconds breath holding.

Inhalers were primed and shaken before use. The spacer devices were pre-treated with 0.05% benzalkonium chloride solution to minimize the influence of electrostatic forces which enhance the deposition of aerosol particles on the spacer walls (11). The subjects wore protective clothing and latex gloves during the administration procedure, in order to prevent contamination of skin and clothes by terbutaline sulphate that could potentially reach subsequent urine collections.

Scintigraphic measurements

Posterior and anterior gamma camera views (General Electric Maxi camera) of the chest and stomach, and a lateral view of the oropharynx were taken immediately after inhalation. The gamma camera was connected to a Nodecrest Micas III data processing system. The geometric mean of the posterior and anterior counts was calculated, and corrections were made for tissue attenuation of gamma rays using the equations of Fleming (12), based upon body thicknesses measured by callipers. Oropharyngeal deposition was taken as the sum of radioactivity recorded over mouth, pharynx, oesophagus and stomach. Radioactivity on the actuator, exhaled air filter and (where appropriate) Nebuhaler® was measured (7, 8). The percentages of the dose in central, intermediate and peripheral lung zones were also determined from computer-generated regions of interest, the lung edges being defined from the 15% contours of ventilation scans obtained using the radioactive inert gas ^{81m}Kr.

Charcoal-block method

Within 10 minutes of inhaling the radiolabelled terbutaline sulphate aerosol, an intravenous injection of 125 μg [$^2H_6$] terbutaline hydrochloride was given as a pharmacokinetic internal standard. A total of 30 g charcoal (Carbomix, Medica Pharmaceuticals) as a suspension was given orally just before and over the two hours post inhalation (5 g in 25 ml water immediately pre-dose and immediately post-dose; 10 g in 50 ml water 1 hour and 2 hours post-dose). Urine was collected for 48 hours in four separate fractions (0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours) and 10 ml samples from these collections, together with a pre-dose sample, were analysed for drug content by a GC-MS method (13). The volunteers fasted for four hours immediately post-dosing and were not permitted to wash their mouths with water for the first hour. The amounts of terbutaline sulphate and deuterated terbutaline hydrochloride in the 48 hour urine collections were quantified, and were used to estimate the percentage of the terbutaline sulphate metered dose deposited in the lungs (4).

Statistical considerations

Lung deposition data were compared between study days using a multiplicative analysis of variance (ANOVA) model in which subject, visit and treatment were the factors. There were two treatment comparisons made for each variable tested: the influence of flow was analysed by comparing results for inhalations at 30 l/min and 180 l/min, and the influence of Nebuhaler® by comparison with inhalation from pMDI at 30 l/min. The methods were compared in a separate analysis where the ratio of the results from the two methods was fitted to an ANOVA model with subject and treatment as the factors.

RESULTS

Radiolabelling measurements

The results of *in-vitro* measurements from the multistage liquid impinger (Figure 1) showed that the particle size distributions of (a) drug from canisters which had not been radiolabelled ("unlabelled drug"), (b) drug from canisters which had been radiolabelled ("labelled drug") and (c) radiolabel were similar. The mean (SD) small particle fraction (particles smaller than 5.5 μm diameter penetrating beyond stage 2 of the impinger) for unlabelled drug was 27.7% (2.8%), compared with 26.5% (4.4%) for labelled drug and 25.7% (3.9%) for the radiolabel. The ratio of the radiolabel small particle fraction to that of the unlabelled drug was 0.93. It was concluded that the radiolabelling procedure had not changed the particle size distribution of terbutaline sulphate, and that the radiotracer was an accurate marker for the presence of the drug substance.

Deposition data

Whole lung deposition expressed as percentages of the metered dose, are compared for gamma scintigraphy and the

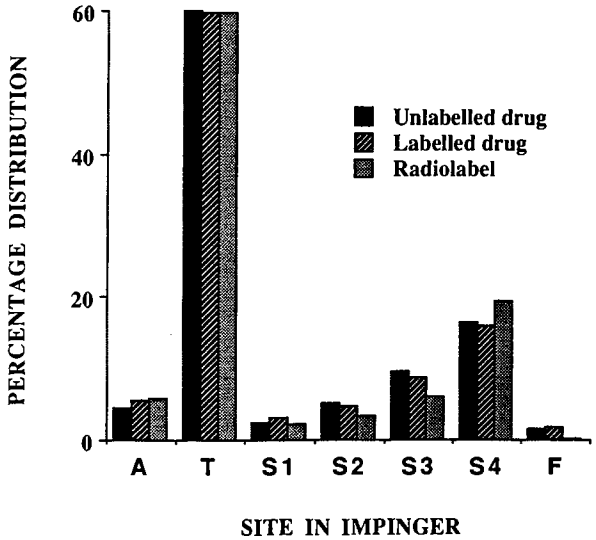

Figure 1. Mean percentage distributions of unlabelled drug (n = 4), labelled drug (n = 12) and radiolabel (n = 11), in a multistage liquid impinger. Sites in the impinger as follows: A = actuator, T = "throat", S1-S4 = stages 1-4, F = final filter. The approximate particle size ranges trapped on the four stages are: S1 25-10 μm, S2 10-5.5 μm, S3 5.5-3.3 μm, S4 3.3-0.8 μm. Forty metered doses were used in each particle size determination.

Table I. Mean (SD) Whole Lung Deposition Data Expressed as Percentages of the Metered Dose Determined by Gamma Scintigraphy and by the Charcoal-Block Method. Inhaled Flows are Targeted Values

	pMDI at 30 l/min	pMDI at 180 l/min	pMDI + Nebuhaler (15 l/min)
Charcoal block	11.2 (4.0)	7.2 (2.2)	33.8 (10.6)
	<---- [P < 0.05] ---->		
		<---------- [P < 0.001] ---------->	
Gamma scintigraphy	10.7 (2.6)	10.4 (5.0)	31.6 (10.1)
	<---- [NS] ---->		
		<---------- [P < 0.001] ---------->	

charcoal-block method in Table I, and a comparison of the two estimates of whole lung deposition is shown in Figure 2. Overall, there was no significant difference between whole lung deposition as determined by the two methods. When the three dosing regimens were considered separately, the two methods gave similar estimates of whole lung deposition for pMDI at a targeted flow of 30 l/min and for Nebuhaler®, but gamma scintigraphy gave a significantly greater estimate of whole lung deposition ($P < 0.01$) than the charcoal-block method for pMDI at a targeted flow of 180 l/min. Both methods showed one individual subject whose whole lung deposition values with Nebuhaler® were relatively low (11.2% by charcoal-block method; 9.5% by gamma scintigraphy), compared to average values of 33.8% and 31.6% respectively.

As shown in Table I, Nebuhaler® significantly increased whole lung deposition compared to the pMDI, as estimated by both methods ($P < 0.001$). Whole lung deposition for the two inhaled flow rates with the pMDI alone differed significantly for the charcoal-block method ($P < 0.05$), but not for gamma scintigraphy.

The fractionation of the dose and the distribution of the dose within the lungs as determined by the gamma scintigraphy are shown in Table II. Nebuhaler® reduced oropharyngeal deposition dramatically, with a mean 40.4% of the dose being deposited in the spacer itself. The regional distribution of the dose within the lungs differed between the three dosing regimens, the peripheral/central zone deposition ratio being significantly reduced ($P < 0.01$) for inhalations from the pMDI at a targeted flow of 180 l/min compared to the other two study days.

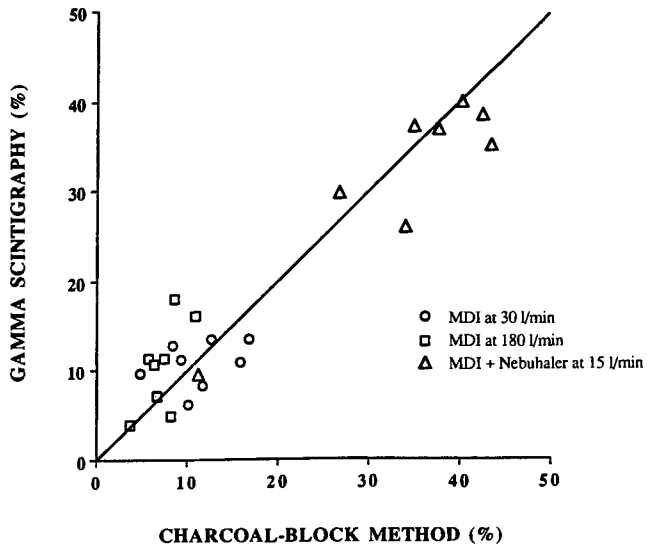

Figure 2. Comparison between gamma scintigraphy and the charcoal-block method for assessing the percentage of the terbutaline sulphate metered dose deposited in the whole lung. The solid line is the line of identity. The given flows are targeted values.

The mean parameters of inhalation (Table III) were close to targeted values, although the mean value for average inhaled flow rate was 151 l/min when a value of 180 l/min was targeted. The inhaled volume for the Nebuhaler (mean of two breaths) was lower than that for pMDI alone. Assessment of the four timed urine collections (Figure 3) showed that the majority of the terbutaline sulphate dose was excreted during the first 12 hours after dosing.

DISCUSSION

Both gamma scintigraphy and the charcoal-block method showed that Nebuhaler® spacer used under optimal laboratory conditions increases whole lung deposition compared to a pMDI, in line with some previous observations (14, 15). The two methods used in the present study gave a good agreement for whole lung deposition except for the fast inhalations from pMDI. This discrepancy may have reflected the more "central" deposition pattern achieved at this flow rate (peripheral zone/central zone deposition ratio 0.96 compared to 1.66 for pMDI at a targeted flow of 30 l/min and 1.56 for Nebuhaler®), and it is possible that material deposited centrally following fast inhalation was detected by gamma scintigraphy, but was then removed from the lungs by mucociliary clearance before it had time to be absorbed into the bloodstream and hence into the urine. Mucociliary clearance of centrally deposited radioaerosol was proposed as a cause of the difference between data obtained by the two techniques in an earlier study (6). These considerations suggest that the two methods measure different aspects of aerosol deposition, although it is not clear whether scintigraphic or charcoal-block data reflect more accurately the clinically effective dose delivered to the target organ.

The charcoal-block method showed a difference in whole lung deposition between studies with the pMDI at slow and fast flows, while gamma scintigraphy failed to do so. Whole lung deposition values as determined by both techniques for the terbutaline sulphate pMDI at the slow

Table II. Percentage Distribution of Metered Dose in Lungs and Oropharynx, and Recovered from the Inhalation Device and Exhaled Air Filter, as Determined by Gamma Scintigraphy. The Fractionation of the Dose Between the Central, Intermediate and Peripheral Lung Zones is also Shown. Data are Mean (SD). Inhaled Flows are Targeted Values

	pMDI at 30 l/min	pMDI at 180 l/min	pMDI + Nebuhaler (15 l/min)
Whole lung	10.7 (2.6)	10.4 (5.0)	31.6 (10.1)
Central lung zone	2.8 (0.8)	4.1 (2.7)	8.4 (3.0)
Intermediate lung zone	3.4 (0.7)	3.2 (1.4)	10.6 (3.7)
Peripheral lung zone	4.5 (1.5)	3.1 (1.1)	12.6 (3.9)
Oropharynx	77.0 (5.5)	79.3 (6.1)	19.5 (14.0)
Actuator	9.4 (3.5)	8.5 (3.5)	8.2 (2.0)
Nebuhaler	—	—	40.4 (9.2)
Exhaled air	2.8 (2.6)	1.8 (2.6)	0.4 (0.2)
Peripheral/central zone ratio	1.66 (0.47)	0.96 (0.45)	1.56 (0.31)

flow were lower than previously observed, a mean value of 16.7% having been recorded in an earlier study on healthy volunteers (9). Other scintigraphic studies (7, 16, 17) have shown increased whole lung deposition at a slow inhaled flow, with a corresponding decrease in oropharyngeal deposition. However, there are few previous data at flows as high as those used in the present study. The vocal cords move further apart as inhaled flow increases (18), and it is possible that this effect would tend to counter the increase in oropharyngeal deposition anticipated from fast inhalation *per se*. The difference between whole lung depositions at slow and very fast inhalation flows from a pMDI may therefore be less than previously supposed.

Nebuhaler® lung deposition values in the present study have been obtained under "best possible laboratory conditions", since retention of aerosol in the device was minimized. The treatment of the inside surfaces of the spacer using benzalkonium chloride reduces the electric field strength and hence losses of particles. Since retention of drug in plastic large volume spacer devices may be affected to considerable extent by electrostatic forces, these deposition data may not be representative of normal use by patients. Drug delivery from the Volumatic® spacer could be increased up to 12-fold when the charge on the spacer was reduced (11).

The data obtained by gamma scintigraphy highlight the importance of attention to three key issues if accurate results are to be obtained. First, it is important to validate the radiolabelling technique in order to ensure that the distribution of the ^{99m}Tc label in different particle size fractions is similar to that of the drug. Second, it must also be checked that the radiolabelling process does not alter the size distribution of the drug. Third, it is vital to make appropriate corrections to recorded count rates to allow for the attenuation of gamma rays that occurs as they pass from the body to the detector. Several methods may be used to correct for tissue attenuation of gamma rays, including injection of a known amount of ^{99m}Tc-labelled macroaggregated albumin (19) or the percentage transmission of ^{99m}Tc gamma rays through the body (20, 21). Our standard technique involves correction factors which vary according to measured body thicknesses. These factors are derived *via* the attenuation equations of Fleming (12) and are used to multiply the observed counts from sites in the body in order to correct for losses in counts resulting from gamma ray attenuation. Typical correction factors are approximately 2.0 for the lungs and oropharynx, and 4.0 for the stomach. Had different factors been applied, then the different scintigraphic data would have been obtained, and the agreement between two techniques could have been less satisfactory. We calculate, for instance, that in a typical pMDI deposition study where a lung deposition value of 15% of the dose was estimated using the above correction factors, a change in the lung correction factor from 2.0 to 1.5 would result in the estimate of lung deposition being reduced to 11.7% of the dose.

Both gamma scintigraphy and the charcoal-block method have their own advantages and disadvantages. Gamma scintigraphy has proved widely applicable to the assessment of drug delivery from pMDIs, powder inhalers and nebulizers (2). The spray characteristics could have

Table III. Average Inhaled Flow, Inhaled Volume and Breath-Holding Pause for the Three Regimens. Data are Mean (SD). Inhaled Flows are Targeted Values

	pMDI at 30 l/min	pMDI at 180 l/min	pMDI + Nebuhaler (15 l/min)
Average inhaled flow rate (l/min)	27 (7)	151 (26)	17 (6)
Inhaled volume (l)	3.2 (1.0)	3.6 (0.6)	1.8 (0.5)
Breath-holding pause (s)	11 (2)	11 (1)	13 (2)

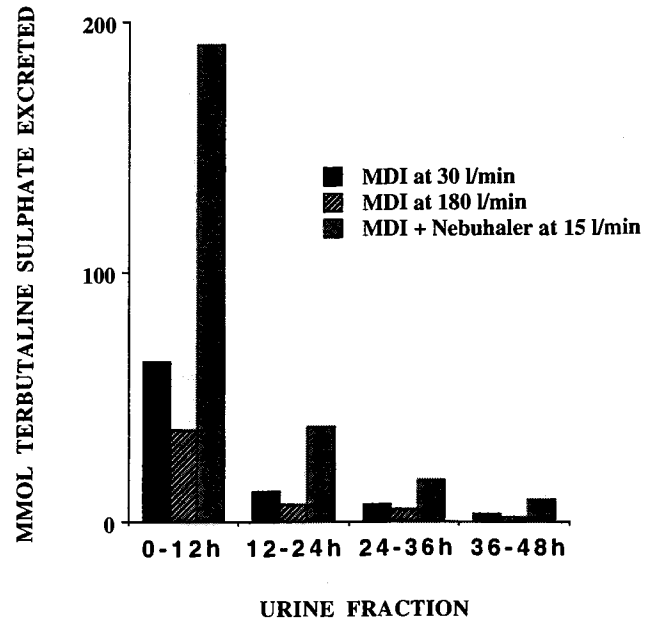

Figure 3. Mean excretion of terbutaline sulphate in four timed urine fractions (0 to 12 hours, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours) for inhalations from pMDI and from pMDI + Nebuhaler. The given flows are targeted values.

been changed during the radiolabelling procedure (22), but this was not the case in the present study. Gamma scintigraphy gives data on both total and regional lung depositions, and a visual representation of the deposition pattern may be obtained as a scintigraphic image. Further, oropharyngeal deposition may be quantified, which may be of particular relevance to control of local and systemic side-effects associated with inhaled corticosteroids (23). Ionising radiation is used, but the radiation doses are small compared to those received in diagnostic radionuclide or X-ray procedures (24).

The charcoal-block method does not require the use of ionising radiation, and uses the intact drug formulation, thus avoiding possible changes to the formulation during radiolabelling. However, no regional lung deposition data are obtained, and no visual scintigraphic image may be acquired. If drug is metabolised in the lung then the method will underestimate absorbed dose. Pharmacokinetic techniques are drug-specific, and for drugs other than terbutaline sulphate and budesonide, the charcoal-block method or another pharmacokinetic technique (25, 26, 27, 28) may be applicable. Some of these other techniques do not permit whole lung deposition to be quantified, but only assess drug levels in plasma and urine. Pharmacokinetic methods of assessing drug delivery often require urine collections, and if these are incomplete then an error will result.

In conclusion, our data support the use of either gamma scintigraphy or the charcoal-block method for assessing whole lung deposition of terbutaline sulphate from a pMDI, used either with or without a spacer device. The choice of method will depend upon prevailing circumstances, and should take into account the inherent advantages and disadvantages that each method possesses.

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