

Site of deposition and absorption of an inhaled hydrophilic solute

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Aims

To characterize the absorption kinetics and bioavailability of an inhaled hydrophilic solute deposited at various sites within the airways.

Methods

Nine healthy nonsmokers received one intravenous, one oropharyngeal and two pulmonary doses of technetium-99 m-labelled diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) in an open and crossover fashion. Pulmonary doses were administered as nebulized large and fine droplet-sized aerosols by Pari and UltraVent nebulizers at fairly rapid and slow inhalation flows, respectively. Plasma concentration-time profiles and 24 h urinary excretion of radioactivity were determined. One dose of ^{99m}Tc-labelled Nanocoll, as a marker of mucociliary clearance (MCC), was also administered by Pari for similar lung deposition as the ^{99m}Tc-DTPA and followed by repeated chest γ -imaging.

Results

Intrapulmonary deposition patterns of ^{99m}Tc-DTPA differed significantly (the mean ratio of penetration index (Pari : UltraVent) was 76% with 95% CI 63%, 91%). However, no differences in rate or extent of ^{99m}Tc-DTPA absorption were detected. Mean absorption time was 1.8 h (mean difference (Pari–UltraVent): –0.1 h with 95% CI –0.6 h, 0.3 h) and the bioavailability was 70% (mean ratio (Pari : UltraVent): 101% with 95% CI 90%, 115%). The pulmonary elimination half-life of ^{99m}Tc-Nanocoll (8 h and 45 min) was significantly longer than that of ^{99m}Tc-DTPA (less than 2 h). The oral bioavailability of ^{99m}Tc-DTPA was estimated to be 3.1%.

Conclusions

The main elimination pathway of the inhaled hydrophilic solute ^{99m}Tc-DTPA from the lungs is *trans*-epithelial absorption. Despite different intrapulmonary radioaerosol deposition patterns, as verified by gamma scintigraphy, no differences in ^{99m}Tc-DTPA absorption kinetics or bioavailability were detected.

Introduction

In order to maximize absorption of inhaled, systemically acting pharmaceuticals, alveolar deposition is generally attempted. Selective alveolar deposition of therapeutic drug aerosols is never achieved in clinical practice and a portion of the inhaled dose is always

deposited in the throat or larger airways. Thus, to characterize the pharmacokinetics of such drugs adequately, deposition outside the alveolar region should be considered.

Because the respiratory tract is recognized as a potential alternative route of administration for systemically

acting drugs with poor oral bioavailability, a more widespread appreciation of pulmonary drug absorption has emerged [1]. Drug transfer across the alveolocapillary barriers has been widely studied, but there is less information on drug absorption in the tracheobronchial airways and throat.

Inhaled drug aerosols are removed from the lungs via one or both of two major pathways, namely the vascular route (involving *trans*-epithelial absorption into the blood) and the mucociliary route (involving mucociliary clearance along the surface of the airways). The predominant elimination pathway and the overall disappearance rate are likely to depend on the initial site of aerosol deposition within the lungs [2, 3].

Much existing knowledge on the rate and extent of pulmonary absorption of inhaled drug aerosols has been acquired using experimental pharmaceuticals. Previous studies have shown striking similarities in the absorption kinetics and bioavailability of inhaled technetium-99 m-labelled diethylene triamine pentaacetic acid (^{99m}Tc -DTPA, MW 492) and the hydrophilic drug terbutaline (MW 225) and insulin (MW 5786). For example, the fate of ^{99m}Tc -DTPA was found to vary with lung volume and breathing pattern [4–7]. The effect of lung expansion on the rate of ^{99m}Tc -DTPA pulmonary disappearance was similar to the increased rate of absorption of inhaled terbutaline observed during physical exercise in normal nonsmokers [8] as well as the increased rate of absorption of insulin delivered during deep as opposed to shallow inhalation [9]. Furthermore, the effect of smoking on the rate of ^{99m}Tc -DTPA pulmonary disappearance [10, 11] was similar to the increased rates of absorption of terbutaline and insulin observed in smokers compared with nonsmokers [12, 13].

Pulmonary absorption of ^{99m}Tc -DTPA can be determined using gamma scintigraphic imaging, provided the radiolabel is not removed from the lungs by a mechanism other than *trans*-epithelial transport [14]. In the alveolar tract, *trans*-epithelial absorption may be the only elimination pathway, but in the conducting airways the radiolabel is probably also removed by MCC. Thus, to estimate accurately the rate and extent of absorption of ^{99m}Tc -DTPA independently of the initial aerosol deposition site within the airways, a method involving the measurement of plasma radioactivity concentrations should be considered [15, 16]. Alternatively, to estimate the extent of absorption, a noninvasive method involving the measurement of urinary excretion of radioactivity could be used [17]. Any contribution to the systemically available radioactivity by the fraction of aerosol filtered off in the throat and swallowed should be negligible

because the gastrointestinal absorption of ^{99m}Tc -DTPA is poor [15, 17–20].

The aim of this work was to compare the rate and extent of absorption of a hydrophilic solute in the oral cavity and the conducting airways and the alveolar tract of the lungs, preferentially.

Methods

Materials

The following materials were used: DTPA (TechneScan DTPA, Mallinckrodt Medical BV, Petten, the Netherlands), human serum albumin nanocolloidal particles (Solco Nanocoll Kit, Nycomed Amersham Sorin, Saluggia, Italy), molybdenum-99 (^{99}Mo) technetium-99 m generator (Ultra-TechneKow FM, Mallinckrodt Medical BV, Petten, the Netherlands), spray pump (VP7/100 S, Valois, Marly-le-Roi, France), Pari nebulizer (Pari LL, Pari GmbH, Starnberg, Germany), UltraVent nebulizer (UltraVent Radioaerosol Delivery System, Mallinckrodt Medical Inc, St. Louis, Missouri, USA), pulsing device (Spira Dosimeter Electro 2, Spira Respiratory Care Center Ltd, Hämeenlinna, Finland), silica gel coated glass fibre sheets (ITLC/SG, Gelman Sciences, Ann Arbor, Michigan, USA), dose calibrator (Capintec CRC-15R, Capintec Inc, Ramsey, New Jersey, USA), gamma counter (Wallac 1480 Wizard 3", Wallac OY, Turku, Finland), and gamma camera (Toshiba GCA-901A, Toshiba Medical Systems, Tochigi, Japan).

Subjects

This study was carried out in nine healthy, nonsmoking men with a mean age of 35 years (range: 24–57 years), a body weight of 82 kg (70–110 kg) and a height of 183 cm (174–192 cm). At inclusion, their mean forced expiratory volume in 1 s (FEV₁) was 96% (75–118%) and vital capacity 96% (83–116%) of predicted normal values [21]. Subjects with recent symptoms of an upper or lower respiratory tract infection were excluded. The study was performed in accordance with the principles stated in the Declaration of Helsinki. Approvals were obtained from the Research Ethics Committee at the University of Lund/Malmö, Sweden, and the Radiation Protection Committee at Malmö University Hospital, Sweden. Subjects were informed about the purpose of the study and gave their written informed consent before inclusion.

Dosing regimens

Each subject received a single dose of about 5 MBq ^{99m}Tc on five different occasions at intervals of at least 2 days. On day 1, an intravenous (i.v.) dose of ^{99m}Tc -DTPA

was administered, followed by four aerosol doses in an open and crossover manner. The aerosol administrations consisted of one dose of ^{99m}Tc -DTPA delivered by a spray pump, one dose of ^{99m}Tc -DTPA delivered by a Pari nebulizer, one dose of ^{99m}Tc -DTPA delivered by an UltraVent nebulizer, and one dose of ^{99m}Tc -Nanocoll delivered by the Pari nebulizer. Subjects were studied in groups of three. Each group was randomly assigned to one of three different administration regimes. The isotope was administered from 08.00 h to 10.00 h, and the procedures were all managed and supervised by the same member of the study team. One subject did not comply with the instructions given and was withdrawn from the study after having received two doses (the i.v. dose of ^{99m}Tc -DTPA and the nebulized dose of ^{99m}Tc -Nanocoll, on separate occasions). The other subjects all completed the study.

Radiopharmaceuticals

On the morning prior to administration, commercially available kits of DTPA and human serum albumin nanocolloidal particles (Nanocoll, with at least 95% of particles having a diameter ≤ 80 nm) were labelled with the gamma ray emitting radionuclide ^{99m}Tc -sodium pertechnetate in physiological saline eluted from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator. Procedures followed the instructions in the package inserts by the respective manufacturer. Depending on the mode of administration, ^{99m}Tc -DTPA solutions of various concentrations of radioactivity were prepared and administered. For i.v. administration, 1 ml of ^{99m}Tc -DTPA of about 5 MBq ml $^{-1}$ (at the time of administration) was injected. The syringe was measured for radioactivity before and after dosing using a dose calibrator. For the oropharyngeal administration, 100 μl of ^{99m}Tc -DTPA of about 50 MBq ml $^{-1}$ was administered as one single puff using a spray pump. For the pulmonary administrations, 2 ml of ^{99m}Tc -DTPA of about 500 MBq ml $^{-1}$ (Pari) or 1000 MBq ml $^{-1}$ (UltraVent) was added to the nebulizer. Likewise, 2 ml of a ^{99m}Tc -Nanocoll-suspension of about 1000 MBq ml $^{-1}$ was added to the Pari nebulizer. While seated in an erect position in front of the gamma camera, subjects inhaled

the nebulized aerosol until a count rate of about 350 s $^{-1}$ over the chest was reached.

Quality control of radiopharmaceuticals

In accordance with recommendations given by the respective manufacturer, procedures used to label DTPA and Nanocoll with ^{99m}Tc were verified using silica gel coated glass fibre sheets. About 4 h after labelling of DTPA, 0.1% was present as reduced hydrolyzed technetium and 0.3% as free pertechnetate. About 4 h after labelling of Nanocoll, 1.0% was present as free pertechnetate.

Administration of radioaerosols

The oropharyngeal dose was administered after actuation of 10 priming doses from the lead-shielded spray pump. When the subject was holding his breath, a single puff of aerosol was sprayed onto the dorsal wall of the pharynx. The pulmonary doses were administered using the lead-shielded nebulizer driven by compressed medical air at a pressure of about 400 kPa. The nebulizer was connected in series to a pulsing device allowing aerosol to be delivered for 300 ms at the beginning of each inhalation (after an initial 100 ml of air had been inhaled). The UltraVent mouth piece was also used with the Pari nebulizer to minimize any contamination of ambient air with radioactivity. A visual indicator assisted subjects in maintaining an inhalation flow of about 0.8 l s $^{-1}$ (Pari) or 0.5 l s $^{-1}$ (UltraVent). In an attempt to compensate for the different nebulizer output rates obtained in experiments before the study, different concentrations of radioaerosol solutions/suspensions were used as described above. However, for the same target count rate to be reached, administration by UltraVent still required a larger number of inhalations than administration by Pari. For each dose, the mean inhalation flow and volume as well as the total number of inhalations triggering aerosol delivery were recorded (Table 1) and actual pulmonary doses (Table 2) assessed scintigraphically, as described below.

Immediately after nebulization, thorough mouth rinsing, repeated 4–6 times using a total of 250 ml of

Radioaerosol	Nebulizer	Inhalation flow	Inhaled volume	Number of inhalations
^{99m}Tc -DTPA	Pari	0.8 (0.6–0.8)	1.2 (0.5–1.8)	6 (3–12)
^{99m}Tc -DTPA	UltraVent	0.5 (0.5–0.5)	0.8 (0.3–1.5)	23 (11–35)
^{99m}Tc -Nanocoll	Pari	0.8 (0.8–0.8)	1.3 (0.6–2.0)	4 (2–9)

Table 1

Mean (range) inhalation flow (l s $^{-1}$), volume (l), and number of aerosol inhalations

Table 2

Mean (CV) penetration index (PI) and deposition of radioactivity in the lungs, trachea/oesophagus, and oral cavity immediately after nebulization and subsequent mouth rinsing

Radioaerosol	Nebulizer	PI	Deposition of radioactivity			
			Lungs (MBq ^{99m}Tc)	Trachea/oesophagus (MBq ^{99m}Tc)	Oral cavity (MBq ^{99m}Tc)	Trachea/oesophagus and oral cavity (% of total)
^{99m}Tc -DTPA	Pari	1.8 (24%)	7.5 (14%)	0.4 (52%)	0.4 (59%)	10
^{99m}Tc -DTPA	UltraVent	2.4 (11%)	5.5 (26%)	0.1 (38%)	<0.1 n.a.	<4
^{99m}Tc -Nanocoll	Pari	1.7 (21%)	12.9 (34%)	0.5 (87%)	0.7 (77%)	9

n.a. = not applicable.

water, was performed to decrease aerosol deposition in the oral cavity, which could interfere with the scintigraphic measurements of the intrapulmonary aerosol deposition pattern.

At the end of the study, the amount of aerosol delivered by the spray pump was measured by weighing replicates of 1, 5, and 10 doses. The aerosol of ^{99m}Tc -DTPA generated by the Pari nebulizer was characterized in terms of mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). A five-stage multistage liquid impinger [22], refrigerated to prevent aerosol evaporation [23], was used. Assessments of droplet size distribution were based on dose to impinger [24]. The MMAD (GSD) of the aerosol of ^{99m}Tc -DTPA generated by the Pari was found to be 2.9 (2.3) μm .

Measurement of radioactivity after ^{99m}Tc -DTPA administration

After each dose of ^{99m}Tc -DTPA, the radioactivity in plasma and urine was measured. Venous blood was sampled before administration and at 5, 10, 20, 40, and 60 min and at 2, 3, 4, 5, and 7 h postdose. The radioactivity in 1 ml of plasma was monitored for 5 min using a gamma counter. Count errors ranged from 0.4% to 7.6%, from 1.2% to 25.8%, and from 0.5% to 2.6%, in samples taken after i.v., oropharyngeal, and pulmonary administration, respectively. Urine was collected for 24 h in three consecutive fractions: 0–6, 6–12, and 12–24 h post administration. For each fraction, the weight of urine was determined and the volume calculated using a density factor of 1.02. Radioactivity was measured in 1 ml during a period of 5 min using a gamma counter. The total number of counts collected per subject and administration resulted in count errors ranging from 0.2% to 1.4%. Radioactivity was corrected for back-

ground radiation and for the physical decay of ^{99m}Tc ($t_{1/2} = 6.02$ h) to the time of administration.

Pharmacokinetic parameters were computed using standard noncompartmental methods. The area under the plasma concentration vs. time curve, AUC, was calculated using the trapezoidal rule to the last measured plasma concentration and the remaining area was extrapolated to infinity, $\text{AUC}_{\text{extrapolated}}$. The latter was calculated using the terminal elimination rate estimated for i.v. administration. The i.v. dose, $\text{Dose}_{\text{i.v.}}$, was determined by measuring the radioactivity in the syringe radioactivity before and after administration. The oropharyngeal dose, $\text{Dose}_{\text{oral}}$, was determined from the radioactivity concentration of the radioaerosol solution administered and, assuming its density to be 1 g ml^{-1} , the mean weight of solution delivered per actuation of the spray pump. The pulmonary dose, $\text{Dose}_{\text{lung}}$, was determined from transmission and aerosol emission scintigrams, as described below. The fraction of radioactivity excreted in urine, f_e , was calculated as the amount excreted, A_e , relative to administered radioactivity ($\text{Dose}_{\text{i.v.}}$, $\text{Dose}_{\text{oral}}$, or $\text{Dose}_{\text{lung}}$, as appropriate). Bioavailability was calculated both as the dose-normalized AUC ratio (F_{AUC}) and as the f_e ratio (F_{f_e}) between a non i.v. and the i.v. route.

Measurement of radioactivity after ^{99m}Tc -DTPA and ^{99m}Tc -Nanocoll administration

For each pulmonary dose of ^{99m}Tc -DTPA or ^{99m}Tc -Nanocoll, chest and head deposition of radioactivity was measured using planar gamma scintigraphy. All images were acquired with the subject in the sitting position in front of a single-headed gamma camera fitted with a low-energy high resolution collimator and with a field of view 40×52 cm. Quality control of the gamma camera was performed in accordance with the manufacturer's

recommendations. A 15% energy window was centred over the 140 keV photo peak. Gamma camera sensitivity was calibrated using a thin ^{99m}Tc source.

On one occasion, prior to administration of ^{99m}Tc -DTPA or ^{99m}Tc -Nanocoll, a transmission image was measured in the posterior view, using a flood source of ^{57}Co . The transmission scintigram was used to correct for tissue attenuation of gamma rays using a previously described method [25], to provide lung contours of each subject, and to delineate regions of interest in the aerosol emission scintigrams.

Immediately after aerosol administration, anterior and posterior images of the chest and head were acquired for 2 min in each view. On average, the anterior chest image was acquired 2 min post aerosol administration and the posterior chest image 4 min later. Deposition of radioactivity in regions of interest (i.e. the oral cavity, the tracheal/oesophageal region, the central lung zone mainly containing the conducting airways, and the peripheral lung zone mainly containing the alveoli) was calculated as the geometric mean of anterior and posterior counts corrected for area-normalized background radioactivity (obtained using a region drawn over the shoulders), for tissue attenuation of gamma rays and for physical decay of ^{99m}Tc back to the time of aerosol administration. The intrapulmonary aerosol deposition pattern of radioactivity within the right lung was established as a penetration index (PI) defined as the ratio of peripheral to central lung zone deposition, calculated on the basis of a previously described method [26]. Total pulmonary deposition ($\text{Dose}_{\text{lung}}$) was calculated as radioactivity in the right lung multiplied by 1.9, as described previously [27].

For each pulmonary dose of ^{99m}Tc -DTPA or ^{99m}Tc -Nanocoll administered using the Pari nebulizer, the amount of radioactivity in the lungs was assessed hourly up to 4 h postdose to allow the pulmonary elimination half-life to be estimated. Thus, in addition to the images obtained immediately after aerosol administration, a posterior 2 min chest image was also acquired at 1, 2, 3, and 4 h post administration. Radioactivity-time curves were obtained for each lung. The amount of radioactivity in the whole lung and peripheral lung zone was calculated for each time-point as the posterior count corrected for the area-normalized background radioactivity, for tissue attenuation of gamma rays and for physical decay of ^{99m}Tc back to the time of aerosol administration.

Statistical analysis

Comparisons between administration modes were made using multiplicative or additive analysis of variance

(ANOVA) models with subject and mode of administration as fixed factors. A difference between two administration modes was expressed as a mean ratio or difference of estimates with 95% confidence intervals (CI) on the ratio or difference. Elimination half-lives were computed by weighted linear regression after converting the individual values to means for each scan time. Separate determinations were made for each mode of administration. Variables derived from data obtained from more than one administration mode were correlated using linear mixed effects modelling. Normal least square regression was used to correlate variables obtained within a mode of administration. All hypothesis testing was done using two-sided alternative hypotheses. A *P* value of less than 5% was considered statistically significant.

Results

The spray pump used delivered a mean (SD) of 100.1 (2.9) mg of ^{99m}Tc -DTPA solution per actuation. The mean (SD) concentration of radioactivity used in the spray pump was 54.6 (4.3) MBq ml⁻¹. The oral bioavailability of ^{99m}Tc -DTPA was estimated to be 3.1% (Table 3). The estimate derived from the fraction of dose excreted in urine (F_{ic}) was considered more reliable than the one calculated from plasma data (F_{AUC}) for the following reasons: plasma radioactivity was low after oropharyngeal administration, the urinary recovery of radioactivity after i.v. administration was complete and urine was collected for a longer period (24 h) than plasma (7 h).

The amount of radioactivity (^{99m}Tc) found in the lungs, trachea/oesophagus, and oral cavity immediately after nebulization and the subsequent mouth rinsing is shown in Table 2. Using UltraVent, the target lung dose of 5 MBq was reasonably well achieved, but with Pari it was exceeded, probably because the target count rate (which was used as a surrogate measure of lung dose) had been set based on experience from clinical procedures involving the use of only UltraVent. Doses to the lung were calculated as the right lung deposition multiplied by 1.9. However, they could equally well have been derived from total deposition in the right and left lungs (data not shown), based on the small (<5%) difference in mean dose estimated by the two methods. Radioactivity in the tracheal/oesophageal and oral cavity regions did not exceed 10% (Pari) and 4% (UltraVent) of the total amount of radioactivity deposited.

For nebulized ^{99m}Tc -DTPA, a more peripheral pulmonary deposition pattern was obtained after administration by UltraVent than when using Pari (Figure 1). The mean CV penetration index (PI) was 2.4 (11%) for

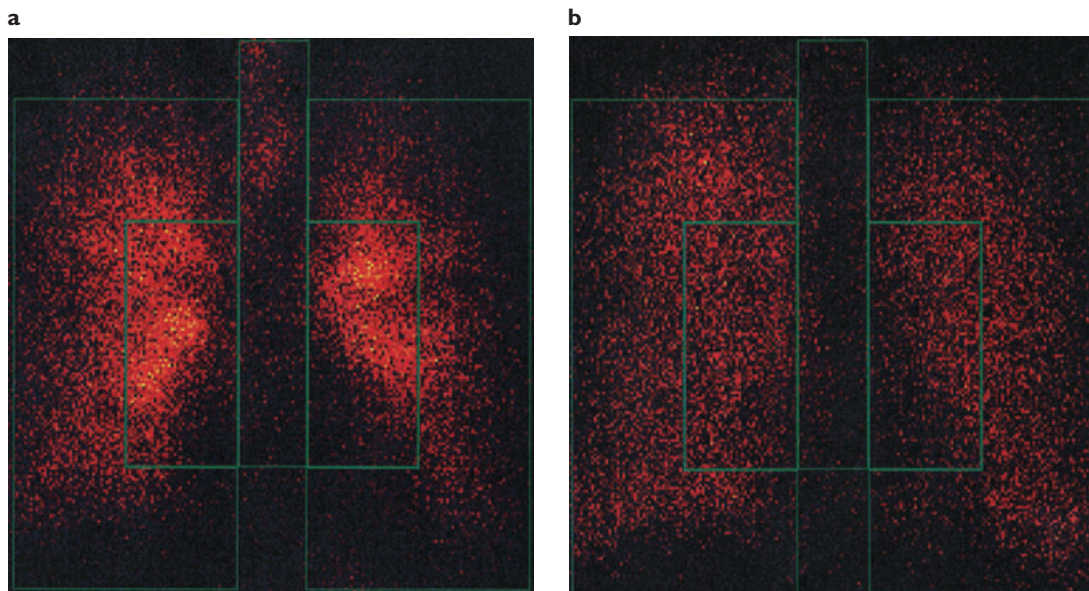
Table 3

Doses given and pharmacokinetic parameters for ^{99m}Tc -DTPA administered to the oropharynx or to the lung (Pari or UltraVent nebulizers), and comparisons calculated as the ratio (Pari : UltraVent) or difference (Pari – UltraVent)

	Oropharynx		Lung (Pari)		Lung (UltraVent)		Comparison (Pari : UltraVent)		
	Mean ^a	Range	Mean ^a	Range	Mean ^a	Range	Ratio (%)	95% CI	P value
Dose (MBq)	5.5	(4.8–6.1)	7.5	(6.1–9.0)	5.5	(3.7–8.4)	137	(109, 171)	0.013
C_{max} (kBq l ⁻¹) ^b	15	(2–57)	163	(92–371)	93	(55–153)	175	(106, 289)	0.034
C_{max}/Dose ((kBq l ⁻¹) MBq ⁻¹)	3	(1–11)	22	(15–54)	17	(12–26)	128	(82, 200)	0.236
AUC (kBq l ⁻¹ h) ^b	103	(16–444)	813	(609–1237)	551	(377–823)	147	(112, 194)	0.012
F_{AUC} (%)	13	(2–49)	73	(56–95)	68	(57–92)	108	(98, 119)	0.110
Ae (MBq) ^b	0.2	(0–0.5)	5.0	(4.2–5.9)	3.6	(2.4–5.2)	138	(107, 179)	0.020
F_{te} (%)	3.1	(1–10)	67	(57–83)	66	(52–83)	101	(90, 115)	0.815
							Difference	95% CI	P value
t_{max} (h)	2.9	(2.0–4.0)	1.2	(0.1–2.0)	1.8	(1.0–4.0)	–0.6	(–1.7, 0.5)	0.229
MAT (h)	3.0	(2.1–3.3)	1.7	(0.7–2.1)	1.8	(0.9–2.5)	–0.1	(–0.6, 0.3)	0.518

^ageometric mean except for t_{max} and MAT (arithmetic means), ^bnot corrected for differences in dose.

MAT mean absorption time, calculated as $MRT_{non-iv.} - MRT_{iv.}$.

**Figure 1**

Pulmonary deposition of radioactivity in a representative subject after administration of ^{99m}Tc -DTPA using Pari (a) or UltraVent (b) nebulizers

UltraVent and 1.8 (24%) for Pari and the PI ratio (Pari : UltraVent) was 76% with a 95% CI of 63% to 91% ($P = 0.005$). For ^{99m}Tc -Nanocoll, also delivered by Pari, the PI was 1.7 (21%).

The pulmonary elimination half-lives of ^{99m}Tc -DTPA and ^{99m}Tc -Nanocoll delivered by the Pari nebulizer are shown in Table 4. There was a five-fold difference in

half-life, measured in the whole lung region, between the two radioaerosols (525 min for ^{99m}Tc -Nanocoll and 104 min for ^{99m}Tc -DTPA). The difference in the half-lives measured in peripheral lung regions was increased to about six-fold (659 min for ^{99m}Tc -Nanocoll and 102 min for ^{99m}Tc -DTPA). The half-life of ^{99m}Tc -DTPA delivered by the UltraVent nebulizer was 109 min

Table 4

Mean elimination half-life in the whole organ and in the peripheral zone of each lung after administration of ^{99m}Tc -Nanocoll and ^{99m}Tc -DTPA, respectively, using the Pari nebulizer

	Elimination half-life (min)		Difference	SEM	95% CI
	^{99m}Tc -Nanocoll	^{99m}Tc -DTPA			
Right lung, whole	513	99	414	53	(311, 517)
Left lung, whole	537	108	429	49	(332, 526)
Right lung, peripheral	715	94	621	140	(347, 894)
Left lung, peripheral	603	111	492	83	(329, 654)

Table 5

Dose given and pharmacokinetic parameters for intravenously administered ^{99m}Tc -DTPA

	Mean ^a	Range
Dose _{iv} (MBq)	5.2	(4.9–5.6)
AUC (kBq l ⁻¹ h)	762	(561–902)
AUC _{extrapolated} (%)	8.1	(3.0–16.4)
<i>t</i> _{1/2} (h)	2.1	(1.5–3.3)
CL (l h ⁻¹)	6.8	(5.6–9.0)
V _{ss} (l)	17	(14–20)
MRT (h)	2.5	(1.7–3.6)
Ae (MBq)	5.3	(4.9–5.8)
fe (%)	101.6	(96.7–109.3)

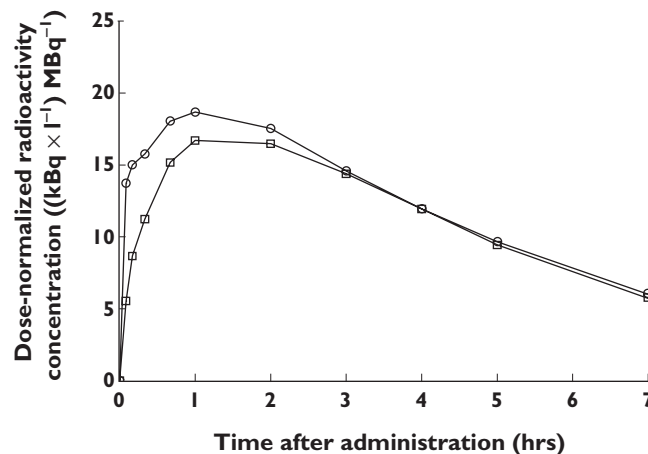
^ageometric mean except for AUC_{extrapolated} and MRT (arithmetic means).

V_{ss} volume of distribution under steady-state conditions, calculated as CL × MRT_{iv}.

MRT mean residence time, calculated as AUMC/AUC where AUMC is the area under the curve of first moment of the plasma concentration vs. time.

(whole lung) and 106 min (peripheral lung zone), values that were similar to those after Pari nebulization.

Pharmacokinetic parameters for ^{99m}Tc -DTPA are given in Tables 3 and 5, and plasma radioactivity vs. time curves for the pulmonary administrations of ^{99m}Tc -DTPA are shown in Figure 2. V_{ss} found after i.v. administration was 17 l, indicating distribution in the extracellular fluid only. The mean AUC_{extrapolated} was about 27% for the oropharyngeal and about 18% for each of the pulmonary administrations. A significantly larger (+47%) mean AUC was found with Pari than with UltraVent (*P* = 0.012). As suggested by the similar pulmonary bioavailability (*F*_{AUC}) estimates of 73% and 68% of lung dose for Pari and UltraVent, respectively (*P* = 0.110), the observed difference in AUC mainly resulted from the difference in lung dose between nebu-

**Figure 2**

Mean plasma concentration of dose-normalized radioactivity vs. time after pulmonary administration of ^{99m}Tc -DTPA nebulized using Pari (○) or UltraVent (□) nebulizers

lizers. By adjusting for dose, the differences in *C*_{max} and Ae also disappeared. Neither *t*_{max} nor mean absorption time was found to differ between the two modes of pulmonary administration, but both parameters appeared to be longer after oropharyngeal than after pulmonary administration.

The maximal contribution to the systemically available amount of radioactivity in the trachea/oesophagus and oral cavity was estimated from the oral bioavailability (*F*_{re}) of 3.1%. It corresponded to less than 1% of the systemically available radioactivity.

Discussion

The different regions of healthy lungs can be targeted by altering one or more factors related to the characteristics of an aerosol (e.g. droplet size or bolus volume), or by altering the pattern of breathing during aerosol inhalation (e.g. inhalation flow, level of lung inflation during aerosol penetration into the respiratory tract, subsequent volume of air inhaled, exhalation flow, or breath holding

time) [3, 28–30]. In the present study, a significant change in intrapulmonary deposition pattern was achieved by varying aerosol droplet size and the flow at which the subjects inhaled the aerosol. Thus a larger aerosol delivered by the Pari nebulizer inhaled fairly rapidly (at an inhalation flow of about 0.8 l min^{-1}) targeted the central lung, and a smaller aerosol delivered by the UltraVent nebulizer inhaled more slowly (at 0.5 l min^{-1}) targeted the peripheral lung. The different intrapulmonary deposition patterns were confirmed by gamma scintigraphy. Based on the PI data, it was concluded that pulmonary deposition was more peripheral after administration using UltraVent than when using Pari. In addition to this difference in intrapulmonary aerosol deposition patterns between nebulizers, the relative amount of radioactivity retained in the tracheal/oesophageal region was larger for the Pari than for the UltraVent nebulizer. This suggests that, although aerosol deposition patterns within the lungs overlapped, different regions of the lungs were targeted by the two modes of administration.

Irrespective of the intrapulmonary aerosol deposition pattern generated, a short MAT of about 1.8 h and a high F of about 70% were observed, which indicate that $^{99\text{m}}\text{Tc}$ -DTPA is rapidly and extensively absorbed across epithelia throughout the lower airways. Since $^{99\text{m}}\text{Tc}$ -DTPA is physiologically inert and distributes almost exclusively to extracellular fluid (confirmed by a value of 17 l obtained for the volume of distribution at steady state), a majority of the remaining 30% not systemically absorbed during 24 h is likely to be removed from the lungs by mucociliary transport. The pulmonary disappearance half-life of the MCC marker $^{99\text{m}}\text{Tc}$ -Nanocoll (8 h and 45 min) produced by the Pari nebulizer was significantly longer than that of $^{99\text{m}}\text{Tc}$ -DTPA (1 h and 44 min with the Pari and 1 h and 49 min with the UltraVent nebulizer). Thus, the MCC of $^{99\text{m}}\text{Tc}$ -DTPA should be less important than *trans*-epithelial absorption. The similarities in the effect of lung expansion or cigarette smoking on the absorption pharmacokinetics of inhaled $^{99\text{m}}\text{Tc}$ -DTPA, terbutaline, and insulin [4–13] suggest that hydrophilic substances are absorbed in a similar manner across epithelia throughout the lower airways.

After administration by the Pari nebulizer, $^{99\text{m}}\text{Tc}$ -DTPA disappeared from the lungs several times faster than $^{99\text{m}}\text{Tc}$ -Nanocoll. Any differences in DTPA and albumin, with respect to their mucus binding properties or their propensities for distribution in airway lining fluid, between the periciliary sol layer and the mucus layer, may have affected the ability of $^{99\text{m}}\text{Tc}$ -Nanocoll to reflect accurately the mucociliary transport of $^{99\text{m}}\text{Tc}$ -

DTPA. To circumvent any such limitations of the methodology in their evaluation of the relative contribution of MCC to the pulmonary elimination of $^{99\text{m}}\text{Tc}$ -DTPA in central airways, Chinnet and coworkers measured the change in background-corrected tracheal/oesophageal radioactivity after administration of $^{99\text{m}}\text{Tc}$ -DTPA [31]. Although central lung radioactivity decreased during the initial 10 min by approximately 13%, no increase in tracheal/oesophageal radioactivity was detected, which seemed to indicate that MCC does not significantly contribute to the pulmonary disappearance of $^{99\text{m}}\text{Tc}$ -DTPA. Values of 104 and 109 min obtained for the pulmonary elimination half-life of $^{99\text{m}}\text{Tc}$ -DTPA in our study were in agreement with those previously reported for healthy subjects (52–107 min) [2, 10, 15, 32–34]. Although the rate of pulmonary elimination of $^{99\text{m}}\text{Tc}$ -labelled human serum albumin in healthy subjects has been determined previously, differences in aerosol formulations and administration techniques prevent direct comparisons between studies. For instance, the $^{99\text{m}}\text{Tc}$ -Nanocoll pulmonary elimination half-life of 525 min obtained in our study with particulate human serum albumin was several times longer than the value of 80 min observed with human serum albumin in solution [2].

For an inhaled hydrophilic drug solute to reach the systemic circulation from the airway lumen, it has to pass through the epithelial lining fluid (ELF) and diffuse across the epithelium. Given the differences in ELF composition and thickness, epithelial cell layer and blood flow between the tracheobronchial and alveolar regions, drug absorption should vary depending on the initial site of aerosol deposition within the lungs. However, in the present study, in which no differences in $^{99\text{m}}\text{Tc}$ -DTPA absorption were detected between administration by the Pari and UltraVent nebulizers, $^{99\text{m}}\text{Tc}$ -DTPA appeared to be absorbed across epithelia throughout the lower airways.

The 24 h urinary recovery of $^{99\text{m}}\text{Tc}$ -DTPA after oropharyngeal administration (3.1%) was in agreement with values of 2.7%, 2.8% and 4.3% found by others [18–20]. The fraction excreted in urine should also reflect the oral bioavailability of $^{99\text{m}}\text{Tc}$ -DTPA because the compound is physiologically inert and eliminated completely via the kidneys [35], a finding confirmed by our i.v. study. The estimate of oral bioavailability derived from urine data was preferred to that from plasma data because the concentration of radioactivity in many of the plasma samples taken after oropharyngeal administration was low. Using the observed oral bioavailability (F_{ic}) of 3.1%, the amount of radioactivity in the oesophagus and oral cavity that could have contributed to the systemically available amount of nebulized

^{99m}Tc -DTPA was estimated to be less than 1%. Stomach radioactivity was not measured in the present study and, thus, any contribution from swallowed, absorbed radioactivity is unknown. However, the degree to which radioactivity in the oral cavity or gastrointestinal tract might have contributed to the systemic radioactivity absorbed from the lungs, was estimated, assuming a nebulizer delivery efficiency of ^{99m}Tc -DTPA as high as that of budesonide in a previous study [36]. In that study, a Pari nebulizer identical to the one in the present study and an aerosol administration technique aiming at maximal pulmonary delivery were used. About 36% of the dose delivered minus the amount of the drug lost due to exhalation and mouth rinsing reached the lungs. Assuming this value for lung deposition, no more than about 6% of radioactivity could have originated from the oral cavity and gastrointestinal tract.

In conclusion, our findings suggest that the main pathway of elimination from the lungs of the inhaled hydrophilic solute ^{99m}Tc -DTPA is *trans*-epithelial absorption. Despite different intrapulmonary radioaerosol deposition patterns, no differences in ^{99m}Tc -DTPA absorption kinetics or bioavailability were detected.

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