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Research Paper

Effects of Sodium Taurocholate on the Absorption of Inhaled ^{99m}Tc-DTPA

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Purpose. The effects of a natural surface-active agent, sodium taurocholate (NaTC), on the absorption of a hydrophilic solute, technetium-99m-labelled diethylene triamine pentaacetic acid (^{99m}Tc-DTPA), deposited at various sites within the airways were evaluated in this open, cross-over, and single-dose study.
Methods. Nine healthy non-smokers received ^{99m}Tc-DTPA with or without the addition of NaTC, administered as an oropharyngeal aerosol and as nebulized large and fine droplet-sized pulmonary aerosols delivered by Pari and UltraVent nebulizers inhaled at fairly rapid and slow flows, respectively. Plasma concentration *versus* time profiles and 24-h urinary excretion of radioactivity were assessed. Further, ^{99m}Tc-labelled human serum albumin nanocolloidal particles (^{99m}Tc-Nanocoll) were administered with or without NaTC by Pari and followed by repeated chest γ-imaging.
Results. NaTC changed no pharmacokinetic parameters for oropharyngeal ^{99m}Tc-DTPA. Independent of intrapulmonary ^{99m}Tc-DTPA deposition pattern, NaTC reduced T_{max} (Pari: −0.8 h; UltraVent: −1.5 h) and mean absorption time (MAT) (−0.4 h; −0.7 h), and increased bioavailability (+13%; +44%) and dose-adjusted C_{max} (+54%; +103%). NaTC decreased the pulmonary ^{99m}Tc-Nanocoll disappearance half-life from 8 h and 45 min to 4 h and 19 min.
Conclusions. Our findings suggest that NaTC increases both rate and extent of ^{99m}Tc-DTPA absorption throughout the lower airways, without changing ^{99m}Tc-DTPA absorption in the oral cavity.

KEY WORDS: aerosol; lung deposition; mucociliary clearance; pharmacokinetics; pulmonary drug absorption enhancement.

INTRODUCTION

Pulmonary absorption of inhaled substances changes with physiological variations and cigarette smoke exposure (1–7). Such variability limits the use of the lungs as a route of delivery for systemically acting drugs with poor bioavailability because plasma concentration, and thereby the biological effects, could be expected to show substantial intra-individual as well as inter-individual variability. One way of reducing the variability could be to increase the pulmonary bioavailability by adding an absorption enhancer to the drug formulation. Surface-active agents have been shown, in rabbits, to increase the absorption rate of inhaled ^{99m}Tc-DTPA, probably by interactions with the alveolar surfactant system, without causing adverse effects on the lung mechanics or gas exchange (8–10). When the natural surface-active agent sodium taurocholate (NaTC, a bile salt) was included in a powder formulation of insulin at a drug-to-agent ratio of 3:1 (w/w), the bioavailability of inhaled insulin, in man, increased from about 6% to about 10% (11,12).

Absorption enhancement by surface-active agents has been studied mainly at the alveolar level. However, in clinical practice, selective alveolar deposition of therapeutic drug aerosols is never achieved. Little is known about the differences in trans-epithelial absorption of inhaled substances at different sites within the airways and the effects of absorption enhancers at those sites (10,13). Thus, we decided to compare the effects of an absorption enhancer on the rate and extent of pulmonary absorption of a hydrophilic solute in the oral cavity and in the lungs, preferentially in the conducting airways and in the alveolar tract. For that purpose, a solution of ^{99m}Tc-DTPA was administered with or without the addition of NaTC to healthy subjects by the use of a spray pump and by either of two nebulizers, Pari and UltraVent, delivering large and fine aerosols, respectively. Plasma radioactivity was assessed during 7 h and radioactivity excreted in urine during 24 h recovered. To investigate whether NaTC affected mucociliary clearance (MCC), a suspension of impermeable, nanocolloidal particles of ^{99m}Tc-labelled human serum albumin (^{99m}Tc-Nanocoll) was administered with and without NaTC by the Pari nebulizer for similar deposition as the ^{99m}Tc-DTPA. Each administration of ^{99m}Tc-Nanocoll was followed by chest γ-imaging during 4 h.

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ABBREVIATIONS: DTPA, diethylene triamine pentaacetic acid; ELF, epithelial lining fluid; MCC, mucociliary clearance; PI, penetration index; ^{99m}Tc, technetium-99m.

MATERIALS AND METHODS

Radiopharmaceutical preparations, radioaerosol administration techniques, and methods used to assess pharmacokinetic and scintigraphic end-points have been presented in detail elsewhere (14) and are only summarized here.

Subjects

Nine healthy, non-smoking men with a mean age of 35 years (range: 24–57 years), body weight of 82 kg (70–110 kg) and height of 183 cm (174–192 cm) participated in this study. At inclusion, their mean forced expiratory volume in 1 s (FEV_1) was 96% (75–118%) and vital capacity 96% (83–116%) of predicted normal values (15). 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 infomed consent before inclusion.

Dosing Regimens

Each subject received a single dose of about 5 MBq ^{99m}Tc on nine occasions at intervals of at least 2 days. On day one, an intravenous (i.v.) dose of ^{99m}Tc-DTPA was administered. [The i.v.-data have been presented previously (14) and are therefore not shown here.] Then, eight aerosol doses were administered in an open and crossover manner. Three of those consisted of ^{99m}Tc-DTPA with and three without the addition of NaTC. They were delivered by a spray pump or either of two nebulizers (Pari and UltraVent). The other two aerosol doses consisted of ^{99m}Tc-Nanocoll with and without NaTC, respectively, delivered by the Pari nebulizer. Subjects were studied in groups of three. Each group was randomly assigned one of three different administration sequences. Administration times ranged from 8 to 10 A.M. One subject did not comply with instructions 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); other subjects received all doses.

Radiopharmaceuticals

Commercially available DTPA and human serum albumin nanocolloidal particles (Nanocoll, at least 95% of particles with a diameter $\leq$ 80 nm) were labelled with the gamma ray emitting radionuclide ^{99m}Tc. On the morning of each study day, a ^{99m}Tc-DTPA solution of varying radioactivity concentration or a ^{99m}Tc-Nanocoll suspension was prepared and, as applicable, NaTC added to a concentration of 0.2 mg $\times$ MBq^{-1} (^{99m}Tc). Prior to the study, target concentration of NaTC was determined in a preliminary experiment as the lowest concentration producing an obvious absorption enhancement in one normal subject after inhalation of ^{99m}Tc-DTPA aerosol delivered by the UltraVent nebulizer.

Quality Control of Radiopharmaceuticals

About 4 h after ^{99m}Tc-labelling of DTPA, 0.1% was present as reduced hydrolyzed technetium and 0.3% as free pertechnetate. When NaTC was added to the solution, 0.5% was present as reduced hydrolyzed technetium and 0.3% as free pertechnetate. About 4 h after ^{99m}Tc-labelling of Nanocoll, 1.0% was present as free pertechnetate which was not changed by the addition of NaTC.

Administration of Radioaerosols

While the subject was holding his breath, 100 μl of ^{99m}Tc-DTPA of about 50 MBq $\times$ ml^{-1} was administered as a single puff of aerosol sprayed onto the dorsal wall of his pharynx. About 2 ml of ^{99m}Tc-DTPA (500 MBq $\times$ ml^{-1} for use with Pari and 1,000 MBq $\times$ ml^{-1} for use with UltraVent) or ^{99m}Tc-Nanocoll (1,000 MBq $\times$ ml^{-1} for use with Pari) was added to the nebulizer connected in series with a pulsing device. While sitting in front of the gamma camera, the subject inhaled the nebulized aerosol until a count rate of about 350 counts $\times$ s^{-1} over his chest was reached. A visual indicator of the inhalation flow assisted subjects in maintaining a flow of about 0.8 l $\times$ s^{-1} (Pari) or 0.5 l $\times$ s^{-1} (UltraVent). Immediately after completed nebulization, thorough mouth rinsing repeated 4–6 times using a total of 2.5 dl of water was performed to reduce the amount of radioactivity in the oral cavity that could otherwise interfere with the scintigraphic measurements of the intrapulmonary aerosol deposition pattern.

After study completion, the amount of aerosol delivered by the spray pump was assessed, by weighing replicates of 1, 5, and 10 doses. Further, the ^{99m}Tc-DTPA aerosols generated by the Pari nebulizer were characterized in terms of mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) using a 5-stage cascade impactor made of aluminium (16).

Assessments (^{99m}Tc-DTPA Administrations Only)

For each dose of ^{99m}Tc-DTPA, radioactivity (^{99m}Tc) in plasma and urine was assessed. Venous blood was sampled before administration and at 5, 10, 20, 40, and 60 min and at 2, 3, 4, 5, and 7 h. Urine was collected during 24 h in three consecutive fractions: 0–6, 6–12, and 12–24 h post administration. Radioactivity was measured and corrected for background radiation and physical decay of ^{99m}Tc ($T_{1/2}$ = 6.02 h) to the time of administration. Pharmacokinetic parameters were assessed using standard non-compartmental methods as follows:

Nomenclature

$Dose_{i.v}$ The actual amount of radioactivity injected, determined by syringe radioactivity measurements before and after administration

$Dose_{oral}$ The actual amount administered to the oropharynx, determined from the average amount of solution delivered per actuation of the spray pump and radioactivity concentration of aerosol solutions administered

Table I. Number of Subjects Studied (n), Mean (Range) Inhalation Flow ($l \times s^{-1}$) and Volume (l), Number of Aerosol Inhalations, Number of Subjects Experiencing Cough During Radioaerosol Nebulization, and Mean (CV) Radioactivity (MBq ^{99m}Tc) in the Lungs, Trachea/Oesophagus and Oral Cavity Immediately after Radioaerosol Inhalation and Subsequent Mouth Rinsing

Radioaerosol	Nebulizer	n	Inhalation flow ($l \times s^{-1}$)	Inhaled volume (l)	Number of inhalations	Cough	Radioactivity (MBq)			Radioactivity (Percentage of total) in trachea/ oesophagus and oral cavity
							Lungs	Trachea/ Oesophagus	Oral cavity	
^{99m}Tc-DTPA[a]	Pari	8	0.8 (0.6–0.8)	1.2 (0.5–1.8)	6 (3–12)	2	7.5 (14%)	0.4 (52%)	0.4 (59%)	10
^{99m}Tc-DTPA +NaTC	Pari	8	0.8 (0.6–0.8)	1.0 (0.5–1.3)	6 (3–11)	8	5.6 (30%)	0.5 (20%)	0.3 (54%)	13
^{99m}Tc-DTPA[a]	UltraVent	8	0.5 (0.5–0.5)	0.8 (0.3–1.5)	23 (11–35)	0	5.5 (26%)	0.1 (38%)	<0.1 *n.a.*	<4
^{99m}Tc-DTPA +NaTC	UltraVent	8	0.5 (0.5–0.5)	0.8 (0.3–1.4)	37 (14–62)	2	4.3 (21%)	0.2 (28%)	<0.1 *n.a.*	<7
^{99m}Tc-Nanocoll[a]	Pari	9	0.8 (0.8–0.8)	1.3 (0.6–2.0)	4 (2–9)	0	12.9 (34%)	0.5 (87%)	0.7 (77%)	9
^{99m}Tc-Nanocoll +NaTC	Pari	8	0.8 (0.8–0.8)	1.1 (0.5–1.8)	5 (3–7)	6	9.5 (36%)	0.6 (59%)	0.6 (39%)	11

[a] From Bondesson *et al.* (14).
n.a. CV not applicable.

$Dose_{lung}$ The actual amount delivered to the lungs by nebulization, determined from the scintigrams
C_{max} Maximal plasma concentration observed
T_{max} Time when C_{max} was observed
k_{el} Terminal elimination rate, calculated for the i.v. administration by linear regression of at least the last three data-points (all data-points—for which the ln $C(t)$ *versus* time curve was linear or approximately linear—were used)
$T_{1/2}$ Terminal half-life, calculated as $\ln 2/k_{el}$
AUC Area under the curve of plasma concentration *versus* time, calculated using the trapezoidal rule to the last time-point (T) of measured plasma concentration (C_T) and the remaining area extrapolated to infinity by C_T/k_{el} ($AUC_{extrapol}$)
AUMC Area under the curve of first moment of the plasma concentration *versus* time, calculated as $AUMC_{0-T}+T\times C_T/k_{el}+C_T/k_{el}^2$
MRT Mean residence time, calculated as AUMC/AUC
MAT Mean absorption time, calculated as $MRT_{non\text{-}i.v.}-MRT_{i.v.}$
Ae Amount excreted in urine
fe Fraction of Dose excreted in urine
F Bioavailability, calculated as the ratio between a non-i.v. administration and the i.v. administration for:
F_{AUC} *(a)* dose-normalized AUC
F_{fe} *(b)* fe

Assessments (^{99m}Tc-DTPA and ^{99m}Tc-Nanocoll Administrations)

For each pulmonary dose of ^{99m}Tc-DTPA or ^{99m}Tc-Nanocoll, chest and head deposition of radioactivity (^{99m}Tc) was assessed with the subject in the sitting position. A transmission scintigram was acquired to correct for tissue attenuation of gamma rays using a previously described method (17), 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 during 2 min in each view. Deposition of radioactivity in regions of interest (i.e., the oral cavity, the tracheal/oesophageal region, the central lung zones mainly containing the conducting airways, and the peripheral lung zones mainly containing the alveoli) was calculated as the geometric mean of anterior and posterior counts subtracted by area-normalized background radioactivity (obtained using a region drawn over the shoulders) and corrected for tissue attenuation of gamma rays and—to the time of aerosol administration—physical decay of ^{99m}Tc.

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 (18). Total pulmonary deposition was calculated as the percentage of radioactivity in the right lung multiplied by 1.9, for reasons previously discussed (19).

Assessments (^{99m}Tc-Nanocoll Administrations Only)

For each pulmonary dose of ^{99m}Tc-Nanocoll, in addition to the anterior and posterior images obtained immediately after aerosol administration, a posterior 2-min chest image

Table II. Penetration Index (Pi) of ^{99m}Tc-DTPA and ^{99m}Tc-Nanocoll Administered without (−) or with (+) NaTC Using either of Two Nebulizers

Radioaerosol	Nebulizer	Mean (CV) (−NaTC)[a]	Mean (CV) (+NaTC)	p value
^{99m}Tc-DTPA	Pari	1.8 (24%)	1.3 (25%)	0.001
^{99m}Tc-DTPA	UltraVent	2.4 (11%)	2.2 (11%)	0.415
^{99m}Tc-Nanocoll	Pari	1.7 (21%)	1.4 (40%)	0.083

[a] From Bondesson *et al.* (14).

Table IIIa. Actual Doses Given and Pharmacokinetic Parameters for Nebulized ^{99m}Tc-DTPA Administered without (−) or with (+) NaTC Using the Pari Nebulizer

	Geometric mean (CV)		Ratio (%)		
	(−NaTC)[a]	(+NaTC)	(+NaTC)/(−NaTC)	95% CI	*p* value
$Dose_{lung}$ (MBq)	7.5 (14%)	5.6 (30%)	75	(62–91)	0.005
C_{max} (kBq × l^{-1})	163 (47%)	189 (40%)	116	(84–161)	0.351
$C_{max}/Dose_{lung}$ ((kBq × l^{-1}) MBq^{-1})	22 (44%)	34 (27%)	154	(117–204)	0.004
AUC (kBq × h × l^{-1})	813 (23%)	754 (24%)	93	(76–114)	0.458
F_{AUC} (%)	73 (23%)	90 (30%)	124	(110–138)	0.001
Ae (MBq)	5.0 (12%)	4.2 (37%)	85	(68–107)	0.146
F_{fe} (%)	67 (12%)	76 (16%)	113	(98–130)	0.087
	Arithmetic mean (SD)		Difference (+NaTC)–(−NaTC)		
T_{max} (h)	1.2 (0.7)	0.4 (0.7)	−0.8	(−1.6–−0.1)	0.030
MAT (h)	1.7 (0.5)	1.3 (0.4)	−0.4	(−0.7–0.0)	0.026

[a] From Bondesson *et al.* (14).

was acquired also at 1, 2, 3, and 4 h post administration and radioactivity–time curves for the whole and peripheral zone of each lung generated.

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 S.r.l., Saluggia, Italy), molybdenum-99m/technetium-99m generator (Ultra-TechneKow FM, Mallincrodt Medical BV, Petten, The Netherlands), NaTC (Natrii taurocholas Eur. kval. D, Apoteket, University Hospital MAS, Malmö, Sweden), spray pump (VP7/100 S, Valois, Marly-le-Roi, France), Pari nebulizer (Pari LL, Pari GmbH, Starnberg, Germany), UltraVent nebulizer (Ultra Vent 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 Siences, Ann Arbor, Michigan, USA), 5-stage cascade impactor (multi-stage liquid impinger, MSLI, Copley Scientific Ltd, Nottingham, UK), dose calibrator (Capintec CRC-15R, Capintec Inc, Ramsey, NJ, USA), gamma counter (Wallac 1480 Wizard 3″, Wallac OY, Turku, Finland), and gamma camera (Toshiba GCA-901A, Toshiba Medical Systems, Japan).

Statistical Considerations

Comparisons between administration modes (i.e., administrations of radioaerosol with and without the addition of NaTC, respectively) were made using multiplicative or additive analysis of variance (ANOVA) models with subject and administration mode as fixed factors. A difference between two administration modes was expressed as a mean

Table IIIb. Actual Doses Given and Pharmacokinetic Parameters for Nebulized ^{99m}Tc-DTPA Administered without (−) or with (+) NaTC Using the Ultravent Nebulizer

	Geometric mean (CV)		Ratio (%)		
	(−NaTC)[a]	(+NaTC)	(+NaTC)/(−NaTC)	95% CI	*p* value
$Dose_{lung}$ (MBq)	5.5 (26%)	4.3 (21%)	78	(65–94)	0.013
C_{max} (kBq × l^{-1})	93 (33%)	147 (31%)	158	(115–219)	0.008
$C_{max}/Dose_{lung}$ ((kBq × l^{-1}) MBq^{-1})	17 (25%)	34 (25%)	203	(154–268)	<0.001
AUC (kBq × h × l^{-1})	551 (26%)	564 (22%)	102	(83–126)	0.816
F_{AUC} (%)	68 (18%)	89 (15%)	131	(117–147)	<0.001
Ae (MBq)	3.6 (23%)	4.1 (13%)	112	(90–141)	0.298
F_{fe} (%)	66 (18%)	95 (31%)	144	(125–165)	<0.001
	Arithmetic mean (SD)		Difference (+NaTC)–(−NaTC)		
T_{max} (h)	1.8 (1.0)	0.3 (0.3)	−1.5	(−2.2–−0.8)	<0.001
MAT (h)	1.8 (0.5)	1.1 (0.3)	−0.7	(−1.1–−0.4)	<0.001

[a] From Bondesson *et al.* (14).

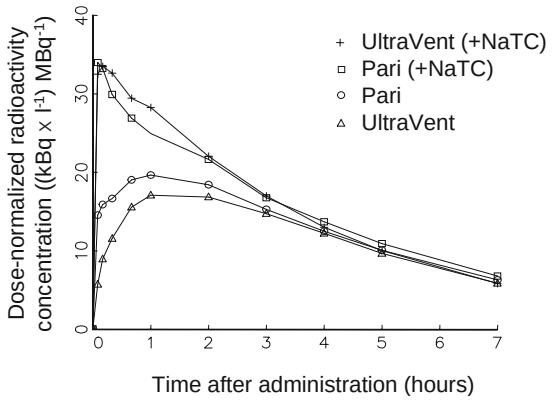

Fig. 1. Mean plasma concentration of dose-normalized radioactivity *versus* time for ^{99m}Tc-DTPA administered with or without the addition of NaTC using two nebulizers: Pari and UltraVent.

ratio or difference of estimates with 95% confidence interval (CI) for the ratio or difference. Pulmonary disappearance half-life was computed by first reducing the individual values to means for each scheduled time of scan and then performing a weighted linear regression on those means. Separate computations were made for each administration mode. Whilst variables derived from data obtained from more than one administration mode were correlated using linear mixed effects modelling, standard linear regression was used to correlate variables obtained within a mode. All hypothesis testing was carried out using two-sided alternative hypotheses. A p value less than 5% was considered statistically significant.

RESULTS

The spray pump used in the study delivered a mean (SD) of 100.1 (2.9) mg of the ^{99m}Tc-DTPA solution or 104.1 (3.1) mg of the NaTC-containing ^{99m}Tc-DTPA solution per actuation. Mean (SD) radioactivity concentration was 54.6 (4.3) MBq × ml^{-1} of the ^{99m}Tc-DTPA solution or 56.4 (4.4) MBq × ml^{-1} of the NaTC-containing ^{99m}Tc-DTPA solution used with the spray pump. The Pari nebulizer delivered aerosols of ^{99m}Tc-DTPA with an MMAD (GSD) of 2.9 (2.3) μm, which increased to 3.3 (2.3) μm after addition of NaTC. Aerosol inhalation parameters, number of subjects experiencing cough during nebulization and radioactivity (^{99m}Tc) found in the lungs, trachea/oesophagus and oral cavity immediately after nebulization and the subsequent mouth rinsing are shown in Table I. With UltraVent, target lung dose (5 MBq) was reached reasonably well, but with Pari it was exceeded in many cases, probably because target count rate (which was used as a surrogate measure of lung dose) had been set based on experience from clinical routine procedures involving the use of only UltraVent. Radioactivity in the tracheal/oesophageal and oral cavity regions after nebulization of ^{99m}Tc-DTPA with or without NaTC using Pari did not exceed 13 and 10%, respectively, or when using UltraVent, 7 and 4%, respectively, of the total amount found in the lungs, trachea/oesophagus and oral cavity.

After oropharyngeal administration, visual inspection of images revealed no differences in oral cavity deposition pattern of ^{99m}Tc-DTPA administered with or without the addition of NaTC. As previously shown, after pulmonary administration, two significantly different intrapulmonary deposition patterns of ^{99m}Tc-DTPA were generated with mean PI 1.8 (Pari) and 2.4 (UltraVent) (p = 0.005) (14). The addition of NaTC to ^{99m}Tc-DTPA delivered by Pari was found to decrease the mean PI to 1.3 (p = 0.001) (Table II). For ^{99m}Tc-DTPA delivered by UltraVent, the addition of NaTC did not cause any change in PI. For ^{99m}Tc-Nanocoll delivered by Pari, a similar, but not statistically significant, trend of decreased PI as for ^{99m}Tc-DTPA was observed. For each of the two pulmonary administration modes, the addition of NaTC resulted in shorter T_{max} and MAT and higher bioavailability (F_{AUC} and F_{fe}) and dose-adjusted maximal plasma concentration (C_{max}) of ^{99m}Tc-DTPA (Tables IIIa and IIIb). Mean plasma radioactivity concentration *versus* time curves for nebulized ^{99m}Tc-DTPA administered with or without the addition of NaTC are shown in Fig. 1. NaTC caused a significant decrease in pulmonary disappearance half-life for ^{99m}Tc-Nanocoll delivered by the Pari nebulizer independent of lung and whether the whole or peripheral zone of the lung was evaluated (Table IV). NaTC changed none of the pharmacokinetic parameters of ^{99m}Tc-DTPA administered to the oropharynx (Table V).

Bioavailability of ^{99m}Tc-DTPA was estimated on the basis of urine data for reasons previously described (14). Oral bioavailability (F_{fe}) of ^{99m}Tc-DTPA administered with or without NaTC was estimated at 3.0 and 3.1%, respectively. Fractions deposited in different regions and corresponding bioavailabilities were used to calculate the maximal contributions to the systemically available amount of radioactivity by depositition in the tracheal/oesophageal and oral cavity regions. It should be less than 1% (at the most 0.6% [i.e., (13 × 0.030)/(13 × 0.030 + 87 × 0.76)] or 0.5% [(i.e., 10 × 0.031)/(10 × 0.031 + 90 × 0.67)] for ^{99m}Tc-DTPA administered with or without NaTC, respectively, when using Pari

Table IV. Mean Pulmonary Disappearance Half-Life (min) in the Whole and in the Peripheral Zone of Each Lung after Administration of ^{99m}Tc-Nanocoll without (−) or with (+) NaTC

	Disappearance half-life				
	(−NaTC)[a]	(+NaTC)	Difference	Standard error	95% CI
Right lung, whole	513	267	246	67	(115–377)
Left lung, whole	537	251	287	59	(170–403)
Right lung, peripheral	715	329	386	150	(92–679)
Left lung, peripheral	603	322	281	100	(86–477)

[a] From Bondesson *et al.* (14).

Table V. Pharmacokinetic Parameters for Oropharyngeal ^{99m}Tc-DTPA Administered without (−) or with (+) NaTC

	Geometric mean (CV)		Ratio (%)		
	(−NaTC)[a]	(+NaTC)	(+NaTC)/(−NaTC)	95% CI	*p* value
C_{max} (kBq × l^{-1})	15 (126%)	14 (322%)	90	(30–273)	0.826
C_{max}/Dose$_{oral}$ ((kBq × l^{-1}) MBq^{-1})	2.8 (134%)	2.3 (314%)	84	(28–247)	0.712
AUC (kBq × h × l^{-1})	103 (125%)	95 (310%)	92	(30–285)	0.869
F_{AUC} (%)	12.8 (148%)	11.0 (322%)	86	(29–258)	0.756
Ae (MBq)	0.17 (93%)	0.18 (135%)	105	(45–249)	0.889
F_{fe} (%)	3.1 (101%)	3.0 (135%)	98	(42–231)	0.966
	Arithmetic mean (SD)		Difference (+NaTC)–(−NaTC)		
T_{max} (h)	2.9 (0.8)	2.4 (1.5)	−0.5	(−1.8–0.7)	0.356
MAT (h)	3.0 (0.4)	3.0 (0.5)	−0.1	(−0.6–0.4)	0.765

[a] From Bondesson *et al.* (14).

and at the most 0.2% [i.e., (7 × 0.030)/(7 × 0.030 + 93 × 0.95) or (4 × 0.031)/(4 × 0.031 + 96 × 0.66) for ^{99m}Tc-DTPA administered with or without NaTC, respectively] when using UltraVent).

DISCUSSION

The effects of a natural surface-active agent, NaTC, on the absorption of ^{99m}Tc-DTPA deposited at various sites within the airways were evaluated. Two different intrapulmonary deposition patterns of ^{99m}Tc-DTPA were generated by varying aerosol droplet size (accomplished through use of two nebulizers: Pari and UltraVent) and the flow at which the aerosol was inhaled. A more peripheral pulmonary deposition pattern was observed after administration using UltraVent than when using Pari. The addition of NaTC to ^{99m}Tc-DTPA was found to increase droplet size of the aerosol delivered by Pari and, as indicated by the decrease in PI, to change the intrapulmonary deposition pattern in such a way that central lung deposition of ^{99m}Tc-DTPA was increased at the expense of peripheral lung deposition. For ^{99m}Tc-DTPA delivered by UltraVent, the addition of NaTC did not cause a change in PI.

Independent of nebulizer used for administration, the addition of NaTC to ^{99m}Tc-DTPA was found to increase both rate and extent of ^{99m}Tc-DTPA absorption. In the oropharynx no absorption enhancing effects on ^{99m}Tc-DTPA were detected. The relative increase in ^{99m}Tc-DTPA bioavailability (fe) was numerically smaller and not significant after administration using Pari than when using UltraVent (+13 *versus* +44%). That could partly be explained by the change in PI observed for Pari (but not for UltraVent), but probably more so by the inherent differences between the conducting airways and the alveolar tract, e.g. in ELF composition and thickness, epithelial cell layer, and blood flow. Main mechanisms underlying absorption enhancement of inhaled insulin by NaTC have been suggested to include opening of tight junctions between adjacent airway epithelial cells (20), but effects on the pulmonary surfactant system cannot be excluded. In fact, the pulmonary surfactant system has been proposed to be a rate-limiting factor for alveolocapillary transfer of ^{99m}Tc-DTPA (21–24). Thus, in the present study, NaTC may have interfered with the functional integrity of surfactant in the lungs.

The pulmonary disappearance half-life of the MCC marker ^{99m}Tc-Nanocoll decreased significantly (from 8 h and 45 min to 4 h and 19 min) due to the addition of NaTC. The fraction of inhaled NaTC that was filtered off and retained by the throat most probably caused local irritation which in turn triggered mucociliary transport, as judged from the higher incidence of cough during nebulization of ^{99m}Tc-DTPA or ^{99m}Tc-Nanocoll with NaTC than during nebulization of ^{99m}Tc-DTPA or ^{99m}Tc-Nanocoll alone.

This study showed that by adding NaTC to the aerosol of ^{99m}Tc-DTPA both rate and extent of ^{99m}Tc-DTPA absorption from the lower airways increased. The effect was greater the more peripheral the deposition. As previously discussed, ^{99m}Tc-DTPA appears to behave similarly to inhaled water-soluble drug substances such as terbutaline and insulin (14). Thus, we may speculate that NaTC would have similar effects on a number of other inhaled hydrophilic drugs. Faster absorption from the lungs may be beneficial in some situations. The plasma profile of inhaled insulin is somewhat faster than after subcutaneous injection (25), but still much slower than the physiological profile. Adding NaTC or other absorption enhancers, once they have been proven safe, to insulin formulations might therefore be an opportunity to improve therapy. Further, increased bioavailability of inhaled drugs could be important for systemically acting substances that are difficult or expensive to produce in large quantities.

In conclusion, NaTC was found to increase both rate and extent of ^{99m}Tc-DTPA absorption throughout the lower airways without changing ^{99m}Tc-DTPA absorption in the oral cavity.

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