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Evaluation of two ^{99m}Tc-DTPA radioaerosols with different characteristics in lung ventilation studies

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Abstract

Two radioaerosol preparations, TechneScan®-DTPA (^{99m}Tc-DTPA, 40 mCi/3 ml; IPEN-CNEN, São Paulo, SP, Brazil) and TechneScan®-DTPA/AEROSOL (^{99m}Tc-DTPA/A, 15 mCi/1.5 ml with 0.5 ml ethanol; Mallinckrodt Medical, St. Louis, MO, USA), were compared in pulmonary ventilation studies in terms of total radiocounts and clearance after inhalation. An aerosol with ethanol is supposed to better distribute the radioparticles in the lungs. Twenty normal nonsmoking volunteers (10 men and 10 women), mean age of 23.2 years (range: 20 to 35 years), were studied. Images were obtained immediately and 30, 60 and 90 min after inhalation. Total and regional counts were obtained and the clearance half-lives of both lungs were determined. There was no difference in total counts between the two types of radioaerosol at any time (mean of ~188,000 cpm for male and female subjects at time zero in both aerosols). The highest count was obtained in the middle region of both lungs (P<0.001) with both preparations. The clearance half-life did not differ between aerosols (mean of ~80-88 min for male and female subjects for both aerosols). Small nonsignificant regional differences were observed. No differences between genders or between right and left lung were observed. ^{99m}Tc-DTPA/A generated the highest output of radioaerosol. ^{99m}Tc-DTPA with alcohol costs approximately five times more than the aerosol without alcohol. The present results show that either kind of aerosol may be adopted routinely for use in pulmonary examinations without affecting diagnosis. We suggest that the amount of 740 mBq (20 mCi) of ^{99m}Tc-DTPA in 1.5 ml saline can be used for routine examinations resulting in reduction of costs in pulmonary ventilation studies without diagnostic impairment.

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- ^{99m}Tc-DTPA

Introduction

Improvements in nebulizer efficiency has led to the widespread use of radioaerosols for the evaluation of global and regional pulmonary ventilation (1). The measurement of pulmonary radioaerosol clearance may indicate the presence of various interstitial diseases and is based on the ability of the alveoli to absorb liquid particles and rapidly remove them (2). The radioaerosol most commonly utilized for this purpose is diethylenetriaminepentaacetic acid (DTPA) labeled with technetium-99m (^{99m}Tc). ^{99m}Tc-DTPA is a hydrophilic molecule with very low lipid solubility. After deposition in the alveoli it diffuses across the interepithelial pores of the epithelium with no apparent active transport mechanism. ^{99m}Tc-DTPA clearance can be used as a measurement of the integrity of the alveolar-capillary barrier (3,4).

Various devices have been used for aerosol generation in the study of pulmonary ventilation (5-11). The most commonly used one is the jet nebulizer. This device generates droplets of a median mass diameter of 1.2 to 6.9 µm and a geometric standard deviation of 1.7 to 2.2 µm, depending mainly on the air flow rate (12). The Ultravent™ system (Mallinckrodt Medical Inc., St. Louis, MO, USA) (13) produces excellent results in intrapulmonary radioaerosol distribution after short periods of inhalation (4,14,15). It generates particles with a median mass diameter of 0.9 µm according to manufacturer specifications (16).

The median mass aerodynamic diameter of radioaerosols generated by commercial nebulizers has been studied in order to characterize particle size distribution. This parameter is relevant since the lung deposition is determined by generated particle size and by particle aerodynamic behavior (17).

The DTPA solution which contains ethanol in its reconstitution formula is considered to increase the efficiency of aerosol distribution by decreasing the surface tension and by increasing the volatility and formation of aerosol droplets, without a change in particle size (14).

The objective of the present study was to compare the lung distribution of two radioaerosols with different reconstitution formulas in pulmonary ventilation studies conducted on healthy individuals of both genders.

Patients and Methods

Twenty healthy nonsmoking volunteers (10 men and 10 women) aged 20 to 35 years (mean: 23.2 years) were included in the present investigation. The study was carried out in the Nuclear Medicine Department, Federal University of São Paulo, Brazil. Subjects had normal clinical examinations, spirometric studies and thoracic radiographs. The study was approved by the Ethics Committee of Hospital São Paulo, Federal University of São Paulo (UNIFESP) and subjects gave informed written consent to participate.

Each volunteer underwent two pulmonary ventilation studies conducted 30 days apart using two different nebulizers, TechneScan® DTPA (^{99m}Tc-DTPA; IPEN-CNEN, São Paulo, SP, Brazil) and TechneScan® DTPA/AEROSOL (^{99m}Tc-DTPA/A, Mallinckrodt).

^{99m}Tc-DTPA was used in the first study with an activity of 1480 MBq in 3 ml physiological saline solution. ^{99m}Tc-DTPA/A was used in the second study with an activity of 555 MBq in 1 ml, with 0.5 ml ethanol (98%, v/v) added after reconstitution. Both studies used the same jet nebulizer (Ultravent™, Mallinckrodt) which generates particles with a median mass diameter of 0.9 µm (16). The same air flow rate was used in both studies.

To estimate the volume of radioactive solution effectively consumed during the study, immediately after inhalation the quantity of residual solution remaining in the cup and in the tubes was determined by weighing the solution of the nebulizer system. Five samples with 3 ml saline solution (solution 1) and five samples with 1 ml saline solution supplemented with 0.5 ml ethanol (solution 2) were nebulized over a period of 5 min.

A gamma camera (Elscint SPX-4HR) was used for image acquisition in a 256 x 256 x 16 matrix. The volunteers were placed in the sitting position and inhaled the radioactive solution for 5 min with nasal obstruction. When inhalation was completed they were placed in the supine position and the images were acquired immediately and 30, 60 and 90 min later in posterior, right and left posterior oblique projections. We used the oblique projection images to detect any existing alterations that were not detected previously. The acquisition time obtained with the first image (400 kcounts) was utilized for subsequent images. All images were stored in a computer for later processing. Background radioactivity was not subtracted due to technical problems concerning its localization.

The total and regional counts were obtained in the posterior projection. Total counts were obtained from a rectangular region of interest drawn automatically over both lungs. Each lung was then divided into three equal areas named upper, middle and lower (Figure 1). All count values were corrected for physical ^{99m}Tc decay. Clearance half-lives measured in minutes in each image were determined by linear regression, plotting the logarithmic function of the total and regional counts against time, as shown in the example in Figure 5.

The Friedman test for analysis of variance was applied to compare the counts obtained with the two types of radioaerosols in each gender at times 0, 30, 60 and 90 min, and in the different regions of the lungs (upper, middle, lower). The Wilcoxon test, which demonstrates the difference between two dependent samples, was applied to compare the total and regional counts obtained with the two radioaerosols (18). The Student *t*-test was used to compare the mean clearance half-lives of the radioaerosols in both lungs, in the different regions and between genders. A level of 5% was fixed for the rejection of the null hypothesis. Significant values are marked with an asterisk.

Results

The anthropometric data of the subjects and the results obtained in the evaluation of pulmonary function are described in Table 1.

A progressive decrease occurred in total counts of ^{99m}Tc-DTPA and ^{99m}Tc-DTPA/A at 30, 60 and 90 min in both the right and left lungs and in both genders (Table 2 and Figure 2). Total counts obtained after ^{99m}Tc-DTPA inhalation for the right and left lungs and for both genders were not significantly different from the radioactive counts obtained after ^{99m}Tc-DTPA/A inhalation (Figure 3).

The highest regional radioactive counts obtained after both ^{99m}Tc-DTPA and ^{99m}Tc-DTPA/A radioaerosol inhalation occurred in the middle region of the lung ($P \leq 0.0001$), followed by the lower and upper regions, respectively. There was no significant difference between males and females for DTPA and DTPA/A or between the two aerosols. Figure 4 shows only male curves because female ones are exactly the same.

Regional and total values for the clearance half-lives of the radioaerosols ranged from 74 to 91 min for both genders and for the upper, middle and lower regions of the

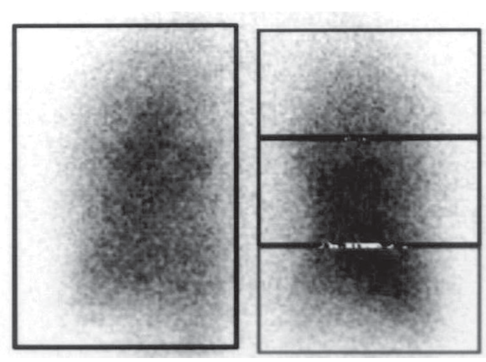

Figure 1. Lung segmentation in posterior projection defining three segments: upper, middle and lower.

Table 1. Anthropometric and ventilation function data of 20 normal individuals.

	Mean ± SD	Median
Age (years)	23.2 ± 3.9	21.5
Height (cm)	170.9 ± 8.9	171.0
Weight (kg)	69.5 ± 11.8	68.3
FVC		
Liter	4.8 ± 1.1	4.6
% predicted	107.9 ± 13.6	104.4
FEV_1		
Liter	3.9 ± 0.8	3.8
% predicted	104.2 ± 11.6	102.0
FEV_1/FVC		
%	83.6 ± 6.4	84.0
% predicted	96.3 ± 6.6	97.7

FEV_1 = forced expiratory volume in one second. FVC = forced vital capacity.

Table 2. Total counts obtained immediately after inhalation (time 0) and after 30, 60 and 90 min, in the right and left lungs of healthy individuals.

Time	DTPA		DTPA/A	
	Female	Male	Female	Male
Right lung				
0 min	188,430 ± 5,937 (3.2)	186,800 ± 14,013 (7.5)	188,004 ± 6,667 (3.5)	187,591 ± 10,080 (5.3)
30 min	134,576 ± 17,508 (13)	136,565 ± 17,190 (12.6)	118,365 ± 22,472 (19.0)	124,049 ± 14,130 (11.4)
60 min	97,087 ± 14,031 (14.4)	102,477 ± 17,941 (17.5)	87,569 ± 19,376 (22.1)	97,756 ± 14,617 (14.9)
90 min	73,661 ± 16,143 (21.9)	80,029 ± 17,679 (22.1)	73,031 ± 20,527 (28.1)	78,669 ± 15,843 (20.1)
Left lung				
0 min	181,693 ± 8,292 (4.5)	181,239 ± 9,344 (5.1)	177,816 ± 6,656 (3.7)	178,433 ± 9,343 (5.2)
30 min	135,021 ± 9,970* (14.8)	130,778 ± 9,600* (7.3)	112,765 ± 18,636 (16.5)	117,814 ± 13,415 (11.4)
60 min	97,660 ± 16,422* (16.8)	98,679 ± 16,786 (17.0)	85,208 ± 15,580 (18.3)	93,451 ± 13,914 (14.9)
90 min	75,746 ± 19,731 (26.0)	75,670 ± 14,855 (19.6)	71,869 ± 19,796 (27.5)	74,943 ± 14,898 (19.9)

DTPA, DTPA/A = diethylenetriaminepentaacetic acid without and with alcohol, respectively. Data are reported as means ± SD with the coefficient of variation in parentheses for 10 females and 10 males for ^{99m}Tc-DTPA and 9 females and 10 males for ^{99m}Tc-DTPA/A radioaerosols. *P<0.05 compared to DTPA/A (Friedman test).

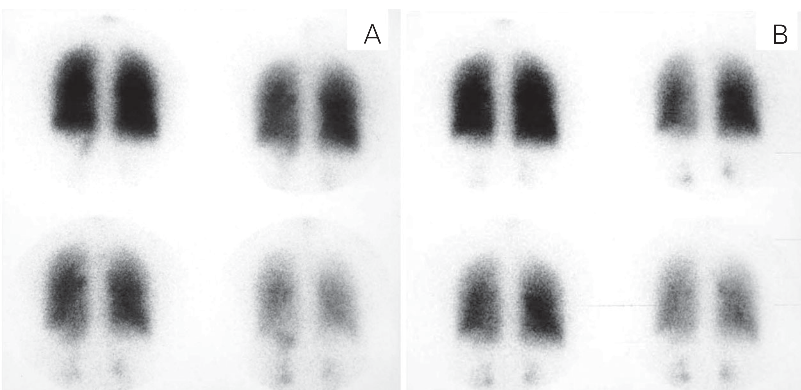

Figure 2. Inhalation study in a 22-year-old normal woman in the posterior projection during the time of the study. Visual inspection shows no difference between DTPA (A) and DTPA/A (B) radioaerosols. Both have the same gray scale. Notice the renal aspect of DTPA elimination. DTPA, DTPA/A = diethylenetriaminepentaacetic acid without and with alcohol, respectively.

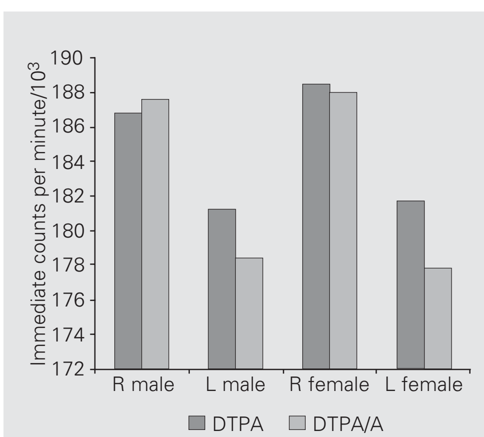

Figure 3. ^{99m}Tc-DTPA and ^{99m}Tc-DTPA/A counts obtained immediately after inhalation (time 0) for the right (R) and the left (L) lungs of 20 healthy individuals. There were no significant difference between ^{99m}Tc-DTPA and ^{99m}Tc-DTPA/A radioaerosols. ^{99m}Tc-DTPA, ^{99m}Tc-DTPA/A = technetium-99m-diethylenetriaminepentaacetic acid without and with alcohol, respectively.

right and left lungs, as shown in Table 3. The clearance half-lives in the upper left lungs differed between males and females. There was no significant difference in clearance half-lives between lungs in the two genders (P>0.05). Figure 5 shows only female curves because both are exactly the same.

The mean quantity of solutions consumed during the nebulization process was 0.78 ± 0.05 ml for solution 1 and 1.16 ± 0.11 ml for solution 2, resulting in flow rates of 0.16 and 0.23 ml/min, respectively, as shown in Table 4.

Discussion

Regional DTPA acquisition values were homogeneously distributed, which is the same as obtained in other studies conducted on normal subjects, in the sitting position (19) or in ventral decubitus (20).

The middle region of the right and left lungs showed the greatest radioaerosol deposition when compared with the lower and upper regions in both genders (P<0.05), an occurrence also observed by Köhn et al. (21). Greater radioactive deposition may be expected to occur in the lower lobes, assuming that this is the pulmonary region which contains the greatest number of alveoli (22-25).

Comparison of our results with previously published data is difficult. Studies of pulmonary ventilation with radioaerosols generally do not describe the regional concentration and usually discuss the pulmonary clearance rate in pulmonary diseases (26-29). Various studies have utilized ^{99m}Tc-DTPA radioaerosol with activities between 740 and 1850 MBq in a volume of 2 to 4 ml saline solution for pulmonary ventilation studies, concentrations similar to those employed in our study (30-34). Some authors have reported the use of higher activities in their investigations (35).

Consumption of a smaller quantity of ^{99m}Tc-DTPA/A than ^{99m}Tc-DTPA was demonstrated during the same inhalation time, suggesting that this preparation achieves more efficient aerosol generation or particle flow. Sirr et al. (14) did not observe any significant alteration in the median mass diameter of the particles obtained from the nebulization of a solution of ^{99m}Tc-DTPA/A radioaerosol containing 20% ethanol in comparison to a solution not containing it. However, a significant increase in the aerosol particles per unit time was observed. These investigators postulated that the introduction of ethanol into the ^{99m}Tc-DTPA/A solution produces a significant decrease in the surface tension of the liquid, mainly increasing the volatility and the efficiency of the aerosol particles.

There was no significant difference in clearance half-life between the two radioaerosols. Sirr et al. (14) also observed no alteration in the clearance time using various concentrations of ethanol (0-40%). The DTPA radioaerosol clearance half-lives obtained in our group of healthy individuals are comparable to those described in the literature, despite the fact that in some investigations the subjects were studied in supine (36), ventral decubitus (20) or sitting (19,37) positions.

No difference in clearance half-lives was observed between the right and left lung, a result also reported by others (15,20,37).

Radioaerosol studies require aerosol particles to be of small size and to have a very low probability of prolonged pulmonary retention. If large quantities of particles impact in the large airways, the penetration and distribution of the particles in the distal air-

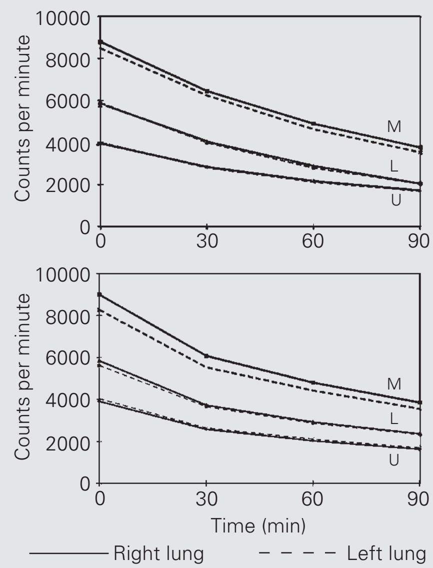

Figure 4. Regional counts obtained immediately after inhalation (time 0) and 30, 60 and 90 min later in the upper (U), middle (M) and lower (L) regions of the right and left lungs of 10 healthy individual males for ^{99m}Tc-DTPA (top) and for ^{99m}Tc-DTPA/A (bottom). ^{99m}Tc-DTPA, ^{99m}Tc-DTPA/A = technetium-99m-diethylenetriaminepentaacetic acid without and with alcohol, respectively.

Table 3. DTPA and DTPA/A radioaerosol clearance half-lives in the upper, middle and lower regions of the right and left lungs in both genders.

	Right lung			Left lung		
	Female	Male	Mean ± SD	Female	Male	Mean ± SD
Upper						
DTPA	79.43	90.63	84.03 ± 7.92	88.61	87.84	88.23 ± 0.54*
DTPA/A	81.82	87.09	84.46 ± 3.73	84.66	87.09	85.88 ± 1.72*
Middle						
DTPA	84.31	89.66	86.99 ± 3.78	89.33	87	88.17 ± 1.65
DTPA/A	80.48	89.37	84.93 ± 6.29	83.16	89.71	86.44 ± 4.63
Lower						
DTPA	83.13	75.9	79.52 ± 5.11	85.58	74.09	79.84 ± 8.12
DTPA/A	75.27	83.41	79.34 ± 5.76	79.15	85.8	82.48 ± 4.70
Total						
DTPA	81.35	89.19	85.27 ± 5.54	86.28	87.02	86.65 ± 0.52
DTPA/A	79.04	86.95	83.00 ± 5.59	83.98	87.27	85.63 ± 2.33

DTPA, DTPA/A = diethylenetriaminepentaacetic acid without and with alcohol, respectively. Data are reported in min.
*$P<0.05$ significant statistical difference between genders (Student *t*-test).

ways will be inadequate, affecting the image obtained (2). In our study, the radioaerosol was distributed homogenously in the various lung fields and radioactivity concentrations were not detected in the upper airways. Also, no impact of the radioaerosol on the components of the nebulizer system was detected, suggesting that particles below 1 µm in diameter were being produced.

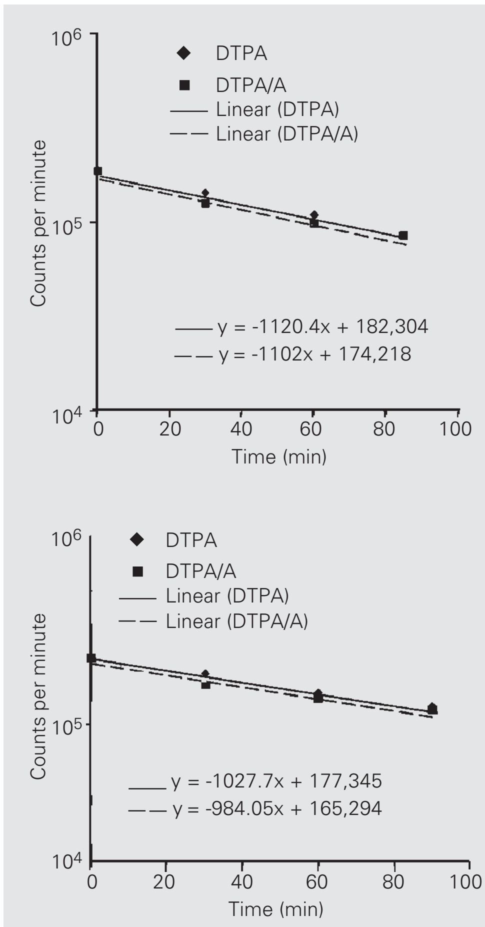

Figure 5. Total counts of the DTPA and DTPA/A radioaerosols for analysis of pulmonary clearance (min) in the right (top) and left (bottom) lungs of female subjects, corrected for 30-, 60- and 90-min decay. DTPA, DTPA/A = diethylenetriaminepentaacetic acid without and with alcohol, respectively.

Table 4. Residual saline solution (RSS) and consumed volume (Δ) generated by the nebulization of saline solution (solution 1) and saline solution with 0.5 ml ethanol added (solution 2).

	Solution 1	RSS	Δ	Solution 2	RSS	Δ
1	3	2.2	0.8	1.5	0.3	1.2
2	3	2.3	0.7	1.5	0.5	1.0
3	3	2.2	0.8	1.5	0.4	1.1
4	3	2.2	0.8	1.5	0.2	1.3
5	3	2.2	0.8	1.5	0.3	1.2
Mean ± SD	3	2.22 ± 0.05	0.78 ± 0.05	1.5	0.34 ± 0.11	1.16 ± 0.11

Data are reported in ml.

The fraction of aerosol particles that enter the airways depends on their size, physical and chemical characteristics of the aerosol, as well as on the morphological and physiological characteristics of the airways, tidal volume and respiratory frequency (38).

Various studies have analyzed the deposition of radioaerosols as a function of tidal volume and respiratory frequency (29,39). Lippmann and Albert (40) have suggested that an adequate pulmonary ventilation image depends on airflow and volume. During our study, we tried to establish identical conditions in the two tests, encouraging the subjects to breathe calmly with a constant airflow, tidal volume and respiratory frequency. This procedure may produce a laminar airflow inside the respiratory airways, preventing turbulence and minimizing the impact of the particles on the upper airways, with a consequent good distribution of the radioactive solution in the pulmonary fields.

The higher level of radioactivity utilized in the preparation of the ^{99m}Tc-DTPA radioaerosol and the greater volume of liquid rejected, 3 ml on average, in each experiment required the maintenance of controlled technical-operational conditions to avoid possible contamination of the environment and of the technicians involved in equipment handling. This rejection suggests that the volume of solution utilized for nebulization was greater than necessary.

An interesting point to be raised concerns costs. The method that uses DTPA associated with alcohol costs approximately five times more than the DTPA aerosol without alcohol. However, based on the flow generated by DPTA without alcohol (0.16 ml/min), a radioactive concentration of 740 MBq in 1.5 ml (20 mCi/1.5 ml) would be sufficient to generate a radioactivity level (2.1 mCi/min) equivalent to that obtained when 1480 MBq in 3 ml (40 mCi/3 ml) is utilized in the routine examinations. This value is approximately equal to 2.3 mCi/ml generated when DTPA with alcohol (0.23 ml/min) is utilized. The radioactive concentration may be estimated as follows: (15 mCi/1.5 ml) x 0.23 ml/min = 2.3 mCi/min. Our suggestion is that ^{99m}Tc-DTPA without alcohol could be prepared as 20 mCi in 1.5 ml saline solution with the same efficiency as the solution prepared before with 40 mCi in 3 ml saline. A vial with ^{99m}Tc-DTPA costs R$19.00 (US$5.28) and can be used for four patients (cost of one patient: US$1.32); a vial of the ^{99m}Tc-DTPA/A costs R$23.00 (US$6.34) and is enough for just one patient. This would greatly reduce the cost of the examination and avoid manipulation of liquid waste which can cause eventual contamination.

We may conclude that there was no statistically significant difference between the total and regional radioactivity counts and the clearance half-lives after the utilization of the ^{99m}Tc-DTPA and ^{99m}Tc-DTPA/A radioaerosols in the two lungs, in healthy individuals of both genders. ^{99m}Tc-DTPA/A showed a greater generation of aerosol which may be explained by the presence of ethanol, although no change in the radioaerosol clearance half-life occurred.

Although the use of 555 MBq of ^{99m}Tc-DTPA/A in pulmonary ventilation studies seems convenient based on its yield efficiency, we suggest that 740 MBq of ^{99m}Tc-DTPA in 1.5 ml saline be used in routine examinations because this would permit a reduction in operational costs, assuming that this volume would give the same diagnostic quality.

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