Effect of Inhaled Furosemide on Lung Clearance of Technetium-99m-DTPA

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The diuretic furosemide has been reported to have a protective effect on allergic asthmatic reactions. This study was performed to investigate the effect of aerosolized furosemide on the lung clearance of ^{99m}Tc-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA). **Methods:** Pulmonary clearance rates of ^{99m}Tc-DTPA were measured by a computerized gamma camera with and without the inhalation of aerosol furosemide in 6 nonsmoking normal volunteers (Group 1), 7 smokers without pulmonary disease (Group 2) and 11 patients with asthma (Group 3). **Results:** None of the six normal volunteers showed significant effects of inhaled furosemide on the ^{99m}Tc-DTPA clearance rates. Three of seven smokers presented an accelerated ^{99m}Tc-DTPA clearance by inhaled furosemide and the other four showed no significant change of ^{99m}Tc-DTPA clearance by furosemide inhalation. However, in 10 of 11 patients with asthma, there was significant suppression of ^{99m}Tc-DTPA clearance by furosemide inhalation. **Conclusion:** Asthmatics possess a furosemide-sensitive mechanism. Pulmonary aerosol scintigraphy with ^{99m}Tc-DTPA will be useful in predicting the effect of inhaled furosemide therapy.

Key Words: technetium-99m-DTPA; asthma; furosemide; aerosol; pulmonary aerosol scintigraphy

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Lung clearance rates of inhaled ^{99m}Tc-DTPA aerosol constitute a sensitive index to evaluate the permeability changes characteristic of the airway epithelium (bronchioles, alveolar ducts, sacs and alveoli) (*1–4*). Recently, a protective effect of inhaled furosemide on asthmatic reactions was proved (*5*) and therapy of inhaled furosemide was found to be useful in some patients with allergic asthma. However, a furosemide-sensitive mechanism in the airway has not been described. It has proven quite difficult to predict the effectiveness of inhaled furosemide in treating patients with asthma. The purpose of this study was to evaluate the effect of inhaled furosemide on the lung clearance rate of ^{99m}Tc-DTPA in patients with asthma.

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MATERIALS AND METHODS

Subjects

In a preliminary study, intrasubject variability of lung clearance rates of inhaled ^{99m}Tc-DTPA was evaluated with eight healthy non-smoking volunteers.

Twenty-four subjects (21 males and 3 females) were divided into three groups. Group 1 was made up of 6 nonsmoking normal volunteers between the ages of 24 and 39 yr (mean age: 29.3 yr). Group 2 consisted of 7 smokers without pulmonary diseases between the ages of 24 and 40 yr (mean age: 31.0 yr) and Group 3 included 11 patients with asthma between the ages of 15 and 36 yr (mean age: 28.8 yr). All asthmatics had characteristic histories of recurrent attacks and positive results of the skin tests and/or the radioallergosorbent tests (RAST). All patients had been free of upper respiratory tract infections for at least 2 wk and had no medication for at least 12 hr prior to the ^{99m}Tc-DTPA clearance measurements. All asthmatics were clinically stable at the time of study. All subjects including 11 asthmatics showed the absence of airway defects by spirometry at the time of this study (Table 1).

Technetium-99m-DTPA Clearance

Technetium-99m-DTPA (555 MBq, 15 mCi) was nebulized using a commercially available nebulizer. The nebulized aerosol was then collected in a 200-liter reservoir bag in order to settle out large droplets, according to the technique described by Hayes et al. (*6*). This system produces a heterodisperse aerosol 1.4 μ in mean diameter. All subjects inhaled the ^{99m}Tc-DTPA aerosol through a mouthpiece in the supine position for about 3 min. After more than 15 k/cpm over lung fields were achieved, posterior views of lung images were obtained with a gamma camera (Siemens ZLC7500, Erlagen, Germany) fitted with a low-energy, all-purpose collimator and interfaced to a computer (Scintipac 700, Shimadzu, Kyoto, Japan). Counts were acquired into a 64 × 64 matrix at 60-sec intervals for 30 min. There were no significant differences between the maximal pulmonary count rates for all individuals in the three groups, ranging from 21.8 to 28.8 k/cpm.

Measurements of ^{99m}Tc-DTPA lung clearance were performed twice in each subject within a 1-wk period. In a preliminary study, measurements of ^{99m}Tc-DTPA clearance rate (%/min) were performed in normal subjects on a separate day to assess the intrasubject variability expressed as percent changes between the first and second study. The mean value ± 2 s.d. of percent changes was defined as the threshold of significant furosemide effect on DTPA clearance rates. For baseline studies, a pulmonary ^{99m}Tc-DTPA inhalation scan was obtained 15 min after the administration of an aerosolized solution of physiological saline as a vehicle of furosemide with the same nebulizer used in furosemide inhalation. To determine the effect of furosemide in this study, a second

TABLE 1
Subjectd Data and Pulmonary Function Test Results

Group	Patient no.	Age/Sex	FVC (liter)	$FEV_{1.0}$ (liter)	$FEV_{1.0\%}$ (%)	V_{50} (liter/sec)	V_{25} (liter/sec)
Normal	1	36/M	3.63	2.89	79.6	4.17	2.89
(Group 1)	2	26/M	4.85	4.17	86.0	4.45	1.25
	3	24/M	4.46	3.53	79.1	3.35	1.38
	4	25/M	5.50	4.46	81.1	3.97	1.90
	5	26/M	4.95	4.18	81.1	4.48	2.10
	6	39/M	3.55	2.92	82.3	4.47	1.11
Smoker	7	27/M	4.00	3.40	85.0	3.96	1.85
(Group 2)	8	36/M	4.72	3.89	82.4	4.40	1.50
	9	40/M	4.38	3.13	71.5	2.50	0.77
	10	24/M	3.52	2.99	84.9	3.67	1.48
	11	29/M	4.78	3.73	78.0	3.24	1.50
	12	35/M	5.42	4.97	91.7	5.10	2.99
	13	26/M	4.00	3.31	82.8	3.56	1.73
Asthma	14	36/M	3.99	3.08	77.1	2.87	1.17
(Group 3)	15	17/F	3.07	2.59	84.4	2.89	1.17
	16	33/M	3.99	2.90	72.6	2.29	0.88
	17	15/M	3.07	3.00	97.7	4.34	2.04
	18	33/M	2.53	2.17	85.8	2.62	1.08
	19	32/M	4.17	3.49	83.7	3.44	1.74
	20	31/M	4.26	3.20	75.1	2.50	1.10
	21	30/M	4.81	3.79	78.7	3.64	1.44
	22	36/M	3.79	3.28	86.5	3.67	1.65
	23	30/M	4.21	3.49	82.8	3.91	1.57
	24	24/F	2.90	2.52	86.8	3.04	1.38

FVC = forced vital capacity; $FEV_{1.0}$ = 1 s forced expiratory volume; $FEV_{1.0\%} = FEV_{1.0}/FVC \times 100\%$.
V_{50} = maximum expiratory flow rate at 50% of the forced vital capacity.
V_{25} = maximum expiratory flow rate at 25% of the forced vital capacity.

^{99m}Tc-DTPA inhalation scan was commenced 15 min after the administration of aerosolized furosemide, consisting of 5 mg diluted in 2 ml of solution. The interval for the second DTPA clearance test was 15 min after furosemide inhalation following the report of Bianco et al. (*5*). Furosemide was nebulized with a commercially available nebulizer (DeVilbiss Model 5610J), which produced heterodisperse aerosols ranging from 0.5 to 5 μm in diameter. The settling bag system was not employed for furosemide inhalation in order to evaluate the effect of furosemide inhaled in the same way as the DTPA aerosol.

Sequential lung images were filtered by nine point smoothing and regions of interest (ROIs) for each lung were determined by the 10% isocontour line of the maximal count in either lung. Time-activity curves were derived from the counts per minute computed in an ROI drawn on each lung field and fitted with a monoexponential line for the first 8 min of the study to minimize the influence of background radioactivity. A least-squares fit was carried out for regression analysis. The clearance rate was calculated from the slope of the disappearance curve and expressed as percentage decrease of the radioactivity per minute (percent/min). The mean value of the clearance rates of the right and left lung fields was used for data analysis.

To quantify the distribution of inhaled aerosol ^{99m}Tc-DTPA, the penetration index (PI) was also calculated for each initial image (1-min image). For each lung, a 10% isocontour line of the maximal count in either lung field was traced on the posterior lung image filtered by nine point smoothing. A single pixel was used as a 10% isocontour line. This rim of activity peripheral to this isocontour was not considered in further calculation. The activity central to this isocontour was stylized into a rectangle, the height and width of which were each divided into thirds. The segment corresponding to the pulmonary hilum was called the hilar zone and the other eight segments the peripheral zone. The ratio of mean activity per pixel in the peripheral zone to that in the corresponding hilar zone was determined to define the PI for the left (PIL) and right lung (PIR) (*7,8*). The mean value of the PI of the right and left lung field was used for data analysis.

Statistical Analysis

Wilcoxon's method was used to evaluate the effect of inhaled furosemide on DTPA clearance and on the PI in each group. The Mann-Whitney U-test was used in two unpaired groups. Significant levels were accepted as p value of less than 0.05.

RESULTS

Intrasubject variability of DTPA clearance rate ranged from 4.0% to 12.7% with a mean ± s.d. of 7.3% ± 3.4% (Table 2). Therefore a mean ± 2 s.d. of less than 14% was determined as an intrasubject variance. The change in ^{99m}Tc-DTPA clearance rates and PI by inhaled furosemide are summarized in Table 3.

In six nonsmoking normal volunteers (Group 1) who received furosemide, ^{99m}Tc-DTPA lung clearance rates

TABLE 2
Reproducibility of ^{99m}Tc-DTPA Clearance Rates in Eight Normal Volunteers

Patient no.	First study	Second study	Variance (%)*
1	0.84	0.80	4.8
2	0.85	0.81	4.0
3	1.01	0.91	9.9
4	0.82	0.92	12.7
5	1.02	0.93	8.8
6	0.97	0.93	4.1
7	1.01	0.91	9.9
8	1.07	1.02	4.5
mean	0.95	0.90	7.3
s.d.	0.10	0.07	3.4

The data are expressed as the clearance rate (%/min).
$* = \frac{\text{value of 1st study} - \text{value of 2nd study}}{\text{value of 1st study}} \times 100.$

were not significantly different before and after furosemide inhalation (0.99% ± 0.11% min versus 0.95% ± 0.15% min n.s., n = 6) (Table 4).

The clearance rate was markedly increased in seven smokers, whereas no significant difference was observed between the baseline study and the study after the administration of furosemide. In Group 2, three of seven smokers showed a significant increase (more than 14%) in DTPA clearance rates after furosemide inhalation (Table 3).

Clearance rates in asthmatic patients were slightly accelerated. In Group 3, 10 of 11 asthmatics showed significant decrease in DTPA clearance rate after furosemide inhalations. All the results of the repeat study for Patients 14, 16 and 18 showed significant decreases in the DTPA clearance rate after furosemide inhalation (Table 3).

In asthmatic patients (Group 3), a significant decrease in the DTPA clearance rate after furosemide inhalation was observed (1.68% ± 0.65% min versus 1.14% ± 0.38% min $p < 0.005$) (Table 4). However, furosemide did not influence the PI of ^{99m}Tc-DTPA in normal controls, smokers and the 11 asthmatics (Table 4).

DISCUSSION

The clearance rate of the inhaled aerosol of ^{99m}Tc-DTPA with less than 2 μm in diameter is mainly limited by the permeability of the airway epithelium. Accelerated DTPA clearance in smokers (*2,9*), as seen in the present study, and in some respiratory disorders (*3,10–14*) are explained by the increased alveolar permeability. Some investigators

TABLE 3
Characteristics of Subjects and Effect of Furosemide on Clearance Rate and Penetration Index of Tc-99m-DTPA

			Clearance rate (%/min)			Penetration index		
	Patient no.	Age/Sex	Baseline	After furosemide	% Change	Baseline	After furosemide	% Change
Normal	1	36/M	1.03	0.93	−9.7	0.65	0.77	18.5
(Group 1)	2	26/M	1.12	1.22	8.9	0.72	0.77	6.9
	3	24/M	1.05	0.97	−7.6	0.79	0.66	−16.5
	4	25/M	1.02	0.89	−12.7	0.82	0.77	−6.1
	5	26/M	0.86	0.75	−12.8	0.80	0.77	−3.8
	6	39/M	0.86	0.91	5.8	0.75	0.75	0
Smoker	7	27/M	2.69	3.05	13.4	0.80	0.76	−5.0
(Group 2)	8	36/M	1.35	2.00	48.1	0.74	0.79	6.8
	9	40/M	5.32	5.29	−0.6	0.74	0.81	9.5
	10	24/M	1.12	2.04	82.1	0.77	0.74	−3.9
	11	29/M	1.40	1.55	10.7	0.75	0.74	1.3
	12	35/M	5.43	5.29	−2.6	0.77	0.74	3.9
	13	26/M	1.61	2.01	24.8	0.66	0.74	12.1
Asthma	14	36/M	1.33	0.78	−41.4	0.80	0.86	7.5
(Group 3)			1.33*	0.64*	−51.9*	0.80*	0.82*	2.5*
	15	17/F	1.24	0.70	−43.6	0.68	0.83	31.7
	16	33/M	1.68	1.29	−23.2	0.78	0.73	−6.4
			1.68*	1.25*	−25.6*	0.79*	0.75*	−5.1*
	17	15/F	1.28	1.06	−17.2	0.73	0.71	−2.7
	18	33/M	1.19	0.92	−22.7	0.86	0.79	−8.1
			1.12*	0.74*	−37.8*	0.80*	0.81*	1.3*
	19	32/M	2.32	1.47	−36.6	0.73	0.81	11.0
	20	31/M	3.36	1.87	−44.4	0.73	0.75	2.7
	21	30/M	1.26	0.84	−33.3	0.77	0.77	0.0
	22	36/M	1.43	0.89	−37.8	0.68	0.61	−10.3
	23	30/M	1.52	1.63	7.0	0.72	0.63	−10.0
	24	24/F	1.82	1.11	−39.0	0.78	0.77	−1.3

*Second ^{99m}Tc-DTPA clearance studies performed 10 mo later.

TABLE 4
Summary of Effect of Furosemide on Clearance Rate and Penetration Index of ^{99m}Tc-DTPA

	Clearance rate (% min)			Penetration index		
	Baseline	Furosemide	p value	Baseline	Furosemide	p value
Normal (Group 1) n = 6	0.99 ± 0.11	0.95 ± 0.15	ns	0.76 ± 0.06	0.75 ± 0.04	ns
Smokers (Group 2) n = 7	2.70 ± 1.89*	3.03 ± 1.61*	ns	0.75 ± 0.04	0.76 ± 0.03	ns
Asthma (Group 3) n = 11	1.68 ± 0.65†	1.14 ± 0.38	p < 0.005	0.75 ± 0.06	0.75 ± 0.08	ns

*p < 0.005 versus normal volunteers (Group 1).
†p < 0.001 versus normal volunteers (Group 1).
The data are expressed as mean ± s.d. ns = not significant.

reported no significant differences between the DTPA clearance of normal subjects and asthmatics (*15–17*). However, various degrees of epithelial damage in asthmatics were detected by bronchial biopsies (*18*) and airway permeability might be expected to increase in patients with asthma from the studies of Bennett and Ilowite (*19*) who controlled the breathing pattern to obtain a primary deposition of aerosol on to the bronchial airway. They proposed a single-compartment model with two pathways by which ^{99m}Tc-DTPA could leave the lung:

$$R_{tot} = e^{-(Km + Kp)t},$$

where R_{tot} is the retention of ^{99m}Tc-DTPA in the lung, Km is the rate constant for mucociliary clearance and Kp is the rate constant for clearance through the airway epithelium. Using this model, increased permeability (Kp) of the bronchial mucosa to ^{99m}Tc-DTPA was proven in patients with asthma (*20*). The clearance rate of ^{99m}Tc-DTPA in our study includes three components: alveolar permeability, bronchial mucosal permeability and mucociliary transport. The clearance rates of ^{99m}Tc-DTPA from bronchial airways and alveoli are quite different (*21,22*); mucociliary activity makes a major contribution to the total clearance of inhaled ^{99m}Tc-DTPA from the tracheobronchial airways. Since the penetration indices were not changed by the inhaled furosemide in each group, the significant effect of furosemide on the clearance of DTPA in asthmatics was not likely to have been caused by changes of aerosol deposition sites. Inhaled furosemide reduced the clearance rate of ^{99m}Tc-DTPA in asthmatics, while a similar significant effect was not seen in healthy volunteers or smokers. The inhaled furosemide seemed to mainly effect the mucosal permeability or mucociliary transport in view of the known pathophysiology of asthma. In contrast to the results seen in patients with asthma, three of seven smokers demonstrated the accelerated clearance rate of ^{99m}Tc-DTPA from the lung after the furosemide inhalation. The most likely cause of this increase in the clearance rate of ^{99m}Tc-DTPA in smokers seems to be the damage of alveolar epithelium by monoxide exposure (*2*). Different mechanisms of the increase in the pulmonary clearance rate of ^{99m}Tc-DTPA in smokers and in asthmatics may result in the different responses to the inhaled furosemide.

Furosemide inhibits the secretion of chloride ions into the bronchial lumen by blocking the co-transport system of sodium and chloride ions on the basolateral membrane of epithelial cells, resulting in the reduction of hypersecretion of bronchial mucosa in asthmatics (*23*). The transepithelial clearance rate of ^{99m}Tc-DTPA follows the equation (*1*):

$$C/C_0 = e^{-(PS/V)t},$$

where C_0 is the initial concentration of inhaled aerosol, C is the concentration at time t, P is the permeability of the membrane, S is the surface area of the membrane and V is the epithelial lining fluid volume. Inhibition of ion and water transport by inhaled furosemide may decrease the permeability (P) or surface-to-volume ratio (S/V) on which aerosol is deposited. This inhibition of ion and water transport may be one of the mechanisms of the furosemide effect on the ^{99m}Tc-DTPA clearance rate in asthmatics, although the exact mechanism of the inhaled furosemide on ^{99m}Tc-DTPA clearance from the lung remains to be studied.

In conclusion, our data indicate that asthmatics have a furosemide-sensitive mechanism and that the aerosol inhalation test with ^{99m}Tc-DTPA may be useful as a tool to predict the effectiveness of furosemide inhalation treatment in asthmatic patients.

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