Diagnostic value of lung clearance of ^{99m}Tc DTPA compared with other non-invasive investigations in *Pneumocystis carinii* pneumonia in AIDS

D S Robinson, D A Cunningham, S Dave, J Fleming, D M Mitchell

Abstract

Various non-invasive investigations were carried out in patients infected with HIV who had respiratory symptoms with and without *pneumocystis* pneumonia (with pneumonia, $n = 13$ (five smokers); without pneumonia, $n = 22$ (13 smokers)). These included chest radiography; lung function tests (forced expiratory volume in one second, forced vital capacity; transfer factor and coefficient for carbon monoxide); arterial blood gas tensions; arterial oxygen saturation at rest and on exercise; and lung clearance of diethylenetriaminepenta-acetic acid labelled with technetium-99m (^{99m}Tc DTPA). The effect of scan time (seven v 45 minutes from peak counts) and subtraction of background counts were examined. There were no significant differences between the two groups in lung function tests or arterial blood gas tensions at rest. The median clearance half time of inhaled ^{99m}Tc DTPA for the first seven minutes from peak counts was 7.2 minutes for patients with pneumocystis pneumonia and 22 minutes for those without. The median arterial oxygen desaturation on exercise was 5% in patients with pneumocystis pneumonia and 2% in those without. ^{99m}Tc DTPA lung clearance was better than the other non-invasive tests in discriminating pneumocystis pneumonia from other pulmonary disorders in patients positive for HIV. A short scan time of seven minutes was as sensitive and specific as the longer scan time of 45 minutes, and this allows the clearance of ^{99m}Tc DTPA to become a rapid screening test.

Pneumocystis pneumonia is the commonest opportunist infection in patients with AIDS, occurring in over 60% of patients.¹ As the pandemic of infection with HIV continues more patients will present with respiratory symptoms.

The range of pulmonary disease in such patients includes increased susceptibility to bacterial infection as well as opportunist infections and malignancy.² Effective prophylaxis against pneumocystis pneumonia with nebulised pentamidine isethionate³ or oral drugs such as co-trimoxazole⁴ may alter this pattern, and empirical treatment of pneumocystis pneumonia in patients presenting with typical symptoms—changes in a

chest radiograph and hypoxaemia⁵—may no longer be tenable as pneumocystis pneumonia becomes less common relative to other infections, and as its presentation is modulated by previous prophylaxis. Diagnosis currently relies on identification of *Pneumocystis carinii* in respiratory secretions.² Sputum induction has proved difficult to establish in some centres so there is a need for an effective screening test to identify patients with symptoms who will probably develop pneumocystis infection before undergoing fiberoptic bronchoscopy.

We assessed the results of pulmonary function tests, arterial blood gas tensions, chest radiology, arterial oxygen saturation before and after exercise, and the clearance of diethylenetriaminepenta-acetic acid labelled with technetium-99m (^{99m}Tc DTPA) in patients positive for HIV with respiratory symptoms.

Patients and methods

Patients positive for HIV presenting with respiratory symptoms were admitted to the study after giving informed consent. A full examination was performed and a full history obtained, particularly about HIV related disease, respiratory disease, and smoking.

The forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured by dry bellows spirometry (Vitalograph, Buckingham). The single breath helium dilution technique was used to measure the carbon monoxide transfer factor (TLCO) and coefficient (KCO), and alveolar volume (VA) (Transfer test model C, PK Morgan, Chatham); all values were corrected for body temperature and haemoglobin concentration and expressed as percentages of predicted values for height and age.⁶

Oxygen saturation when the patient was breathing room air was measured with a finger probe pulse oximeter (Novamatrix, Wallingford, Connecticut) when the patient was at rest and after he had performed exercise up and down a step to achieve twice the resting heart rate or maximal effort.

Chest radiographs were reviewed by a radiologist unaware of the data on clearance of ^{99m}Tc DTPA or of the bronchoscopic diagnosis. All patients had the lung clearance of ^{99m}Tc DTPA measured within 48 hours after admission and before fiberoptic bronchoscopy. Arterial blood gas tensions were measured on admission. When symptoms did not improve with antibacterial treatment

Department of
Respiratory Medicine
D S Robinson
J Fleming
D M Mitchell

Department of
Radiology
D A Cunningham
S Dave

St Mary's Hospital,
London W2 1NY

Reprint requests to:
Dr Mitchell.

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Table 1 Stage of HIV disease (Centers for Disease Control classification) in 35 patients with respiratory symptoms

	Centers for Disease Control classification*			
	II	IVa and IVc2	IVc1	IVd
Pneumocystis pneumonia:				
Present (n = 13)	2	7	3	1
Absent (n = 22)	3	9	7	3

* II—Asymptomatic infection; IVa—constitutional disease; IVc2—other specified secondary infectious diseases; IVc1—specific secondary infections listed by CDC (for example, pneumocystis pneumonia); IVd—secondary cancers (for example, Kaposi sarcoma).

patients underwent fiberoptic bronchoscopy with bronchoalveolar lavage.

Sputum and blood samples were taken for virological and bacteriological examination.

LUNG CLEARANCE OF ^{99m}Tc DTPA

^{99m}Tc DTPA (1000 MBq) in 3 ml saline was placed in an Optimist nebuliser with a separator (Medicaid, Pagham) driven by air flowing at 6 l/m. Patients were seated with their back to a gamma camera and inhaled the aerosol through a mouthpiece for four minutes while wearing a nose clip. The total count rate at the end of this period was roughly 2000 counts per second. Data were acquired at one frame a minute for 45 minutes with a large field of view gamma camera and a general purpose collimator linked to a dedicated computer.

Data were analysed separately for each lung with background counts from a region between the two kidneys subtracted and included.⁷ Curves were plotted on a semilog scale and judged visually to be either monoexponential or biexponential. A straight line was fitted to the curve by the computer with a least squares fit between two points being determined by the operator. When the curve was biexponential the slow component was subtracted from the original curve and a second straight line fitted to the new stripped data. Data for the first seven minutes after peak activity were also analysed. These curves were monoexponential and a single straight line was fitted.

Table 2 Median values and 95% confidence intervals for difference for variables significantly different between patients positive for HIV with and without pneumocystis pneumonia

Variable	<i>Pneumocystic pneumonia</i>		95% confidence interval of difference	p
	<i>Present (n = 13)</i>	<i>Absent (n = 22)</i>		
<i>Arterial oxygen desaturation on exercise (%)</i>				
All patients	5	2	0 to 5	0.04
<i>Clearance half time of ^{99m}Tc DTPA (min)</i>				
All patients:				
7 minutes after peak counts:				
Background included	9.6	24.0	4.3 to 20.0	0.001
Background subtracted	7.2	20.0	5.0 to 18.2	0.0007
45 minutes after peak counts:				
Background included	10.7	27.0	10.0 to 22.0	0.0002
Background subtracted	9.0	23.0	8.5 to 18.1	0.0004
Smokers:				
7 minutes after peak counts:				
Background included	9.6	19.0	0.0 to 18.0	0.04
Background subtracted	7.2	15.5	1.0 to 15.8	0.02
45 minutes after peak counts:				
Background included	10.7	24.5	5.0 to 22.0	0.01
Background subtracted	9.0	20.0	2.0 to 16.1	0.02

Each lung was divided into upper and lower zones; curves generated for each zone were assessed visually to determine whether they were biexponential or monoexponential.

STATISTICAL ANALYSIS

The Mann-Whitney U test was used to compare data from patients with and without pneumocystis pneumonia. Receiver operator curves were constructed for ^{99m}Tc DTPA clearance half times by plotting sensitivity versus (1 – specificity) for a range of cut-off values.

Results

Thirty five homosexual men positive for HIV were studied. Their mean age was 38.7 years (range 21–58), and 18 were current smokers. Table 1 shows the stage of HIV disease at inclusion.

Thirteen patients (five smokers) had pneumocystis pneumonia confirmed by fiberoptic bronchoscopy. Twenty two patients (13 smokers) did not have pneumocystis pneumonia; 12 had fiberoptic bronchoscopy at which *P. carinii* was not isolated (three had endobronchial Kaposi's sarcoma, one had tuberculosis, six had bacterial pneumonia), and 10 had symptoms that resolved rapidly on treatment with either erythromycin or amoxycillin. None of these patients was treated with drugs effective against pneumocystis pneumonia.

There was no significant difference between the two groups in respiratory rate (median 20 for both groups); FEV₁ (85% and 93% of predicted values for those with and without pneumonia respectively); FVC (82% and 92%); TLC (61% and 57%); Kco (71% and 78%); arterial oxygen tension (10.4 and 10.5 kPa); or arterial carbon dioxide tension (4.8 and 5.0 kPa).

Chest radiographs from eight patients with pneumocystis pneumonia had changes suggestive of opportunist infection and two were normal (in three cases chest radiographs were not available). Eighteen of the radiographs

Figure 1 Clearance half times (in first seven minutes after peak counts without background subtraction) in patients with and without pneumocystis pneumonia. Open symbols are smokers, closed symbols non-smokers.

from the patients without pneumocystis pneumonia were normal, one showed lobar consolidation, two showed nodular shadowing compatible with Kaposi's sarcoma; and one had bilateral hilar shadowing compatible with pneumocystis pneumonia.

OXYGEN DESATURATION AND CLEARANCE OF ^{99m}Tc DTPA

Oxygen desaturation on exercise and clearance half times of ^{99m}Tc DTPA were significantly reduced in patients with pneumocystis pneumonia (table 2). Although smokers had lower clearance half times in both groups, the differences between the smokers and non-smokers with and without pneumocystis pneumonia remained significant. There was, however, overlap in the findings between the two groups (table 2 and figure 1).

Clearance half times of ^{99m}Tc DTPA calculated from the first seven minutes after peak counts gave equal discrimination between the two groups as did the 45 minute clearance half time. Figure 2 shows examples of clearance curves of ^{99m}Tc DTPA from patients with and without pneumocystis pneumonia. Receiver operator curves showed the optimal cut off value for the clearance half time in the seven minutes after peak counts to be 10 minutes: this gave a sensitivity of 92% and specificity of 82% in diagnosing pneumocystis pneumonia (figure 3).

Data on the whole lung collected over 45

Figure 2 Lung clearance curves of ^{99m}Tc DTPA of log counts versus time in patients positive for HIV (a) without pneumocystis pneumonia (monoexponential) and (b) with pneumocystis pneumonia (biexponential). Fast half time = nine minutes, slow half time = 30 minutes (45 minutes after peak counts).

minutes showed a biphasic clearance in 12 of the patients with pneumocystis pneumonia and in four of those without, all of whom were heavy smokers. Monophasic clearance was seen in one patient with pneumocystis pneumonia and in 17 of those without. Thus the shape of the clearance curve gave equivalent sensitivity and specificity to the seven minute data as a diagnostic test for pneumocystis pneumonia. Analysis of the shape of the curves from upper and lower zones showed that only patients with pneumocystis pneumonia had biphasic clearance from both upper and lower zones of the lung. Eight of the patients without pneumonia (five smokers) had biphasic clearance from the upper zones, but none had biphasic clearance from the lower zones. When upper and lower zones were analysed separately the sensitivity of biphasic clearance in diagnosing pneumocystis pneumonia was 70% and the specificity 100%. When clearance time and regional analysis of the shape of the curve were combined the sensitivity was 92% and the specificity 100%. The sensitivity of radiographic diagnosis in diagnosing pneumocystis pneumonia was 78% and the specificity 95%. With a cut off value of 3.5% the sensitivity of arterial oxygen desaturation on exercise was 71% and the specificity 100%.

Background subtraction shortened all the clearance half times but did not increase discrimination in terms of either the shape of the curve or the clearance time. There was no difference in the clearance half times of ^{99m}Tc DTPA between patients with endobronchial Kaposi's sarcoma (21, 23, and 24 minutes) and the other patients without pneumocystis pneumonia (median 22 minutes).

Discussion

In our study of non-invasive tests in patients positive for HIV presenting with respiratory symptoms lung clearance of ^{99m}Tc DTPA was the best in distinguishing patients with pneumocystis pneumonia from those without. Many non-invasive tests have been used to try to distinguish pneumocystis pneumonia from other causes of respiratory symptoms. None has proved entirely successful. A chest radiograph may be normal in 5–10% of cases,^{8,9} but atypical features occur in up to 5% and other conditions may mimic pneumocystis pneumonia.²

Figure 3 Receiver operator curves for clearance half times of ^{99m}Tc DTPA in seven and 45 minutes after peak counts (background counts subtracted and included). Maximal resolution (top left corner) gives sensitivity of 92% and specificity of 82%.

Abnormalities in lung function occur in most patients with pneumocystis pneumonia^{10,11} but a reduction in FVC, TLC, and Kco also occur in patients with AIDS without respiratory symptoms.¹¹ Arterial hypoxaemia occurs in up to 80% of patients with pneumocystis pneumonia¹² but is a non-specific finding in pulmonary infection and may not be present early in the course of the pneumonia.⁵

Arterial oxygen desaturation occurs on exercise in patients with HIV infection and pneumocystis pneumonia¹³ and is a useful screening test for such pneumonia in HIV positive patients with respiratory symptoms and a normal chest radiograph.¹⁴ In our patients this test was specific but not as sensitive as lung clearance of ^{99m}Tc DTPA.

A characteristic feature of pneumocystis pneumonia is widespread alveolar infiltration and attachment of the organism to type 1 pneumocytes.¹⁵ Changes in alveolar permeability can be detected by changes in the ratio of lung to blood clearance of inhaled ^{99m}Tc DTPA.¹⁶ When alveolar damage is severe clearance is increased above normal values and is biphasic with rapid, early clearance from the most damaged alveoli. Biphasic curves have been reported in pneumocystis pneumonia¹⁷ and in the adult respiratory distress syndrome.¹⁶ Other insults to the lung, such as smoking,¹⁸ may increase the rate of clearance of ^{99m}Tc DTPA from the lung but do not result in a biphasic curve. This distinction has been used to separate HIV positive patients with pneumocystis pneumonia from those without.

Our results confirmed the increased clearance in patients who are HIV positive and have pneumocystis pneumonia and showed that the shape of the clearance curve is almost invariably biphasic. We were unable to confirm the absolute distinction between patients with and without pneumocystis pneumonia reported by O'Doherty *et al.*,¹⁷ perhaps because of differences in the methods used. The particle size quoted for the Venticis nebuliser has a mass median diameter of 0.9 μm whereas that of our nebulising system has a mass median diameter of 1.4 μm at a flow rate of 10 l/min.¹⁹ We used a flow rate of 6 l/min because a rate of 10 l/min was difficult to maintain owing to the resistance within the separator. The aerosol particle size in our study was therefore probably larger than 1.4 μm , and undoubtedly greater than that in the study of O'Doherty *et al.*¹⁷ A second important difference between our study and that of O'Doherty *et al.* is in the control group. All our patients were HIV positive with a fairly advanced stage of disease. All had respiratory symptoms and over half of them smoked cigarettes. Thus although our control subjects were clinically appropriate, they did not have normal lung function. Both smoking and long term HIV infection increase lung permeability measured by clearance of ^{99m}Tc DTPA.¹⁷ Therefore it is not surprising that some control patients had rapid clearance with values that overlapped those in the pneumocystis pneumonia group, or that some control subjects also showed a biphasic pattern when the whole lung was analysed. Smoking

increases the permeability of the lungs predominantly in the upper zones; our results confirm this: none of the patients without pneumonia who smoked had a biphasic clearance from the lower zones when these were analysed separately.

Subtraction of background counts may be important in analysing lung clearance of ^{99m}Tc DTPA because rising activity in the blood pool within the lung will cause an apparent reduction in clearance from the lung. We measured background counts in a region between the two kidneys because this approximates well to activity in the blood pool.⁷ The more complicated method of subtracting blood pool counts by using an intravenous injection of ^{99m}Tc DTPA²⁰ would have prolonged the study considerably and we found that it was no better in assessing vascular activity within the lung than was a simple measurement in the region between the two kidneys.

We found that lung clearance of ^{99m}Tc DTPA discriminates better than spirometry, TLC, and arterial blood gas tensions between pneumocystis pneumonia and other causes of respiratory symptoms in HIV positive patients. A seven minute scan time provides excellent sensitivity with good specificity and is a practicable screening test in such patients. Whether the ability to discriminate between the two conditions would have been improved further by using a system with a higher flow rate and a smaller particle size requires further investigation. The combination of lung clearance of ^{99m}Tc DTPA and oxygen desaturation on exercise seemed to be the most useful screening test in selecting patients for further investigation for possible pneumocystis pneumonia.

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