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Technetium-99m-DTPA aerosol scintigraphy in amiodarone induced pulmonary toxicity in comparison with Ga-67 scintigraphy

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Amiodarone hydrochloride, which is used in life-threatening cardiac tachyarrhythmia, has been known to cause amiodarone induced pulmonary toxicity (AIPT) as a complication. In this study we aimed to investigate the clinical value of technetium-99m diethylene triamine penta-acetic acid (DTPA) aerosol lung scintigraphy in patients with AIPT in comparison with gallium-67 (Ga-67) scan. The study group included 26 cases, 7 patients with diagnosis of AIPT (Group A), 8 patients receiving amiodarone therapy but without AIPT (Group B) and 11 healthy subjects as a control group (Group C). All patients underwent Ga-67 and Tc-99m-DTPA aerosol scintigraphy in addition to various laboratory tests, Ga-67 scintigraphy was positive in 4 of 7 AIPT patients but quite normal in Group B. A positive correlation was found ($r = 0.52$, $p < 0.05$) between kep values determined by Tc-99m-DTPA aerosol scintigraphy and the cumulative dose of amiodarone. The mean kep values were 2.04% ± 0.85%/min, 1.30% ± 0.42%/min and 0.86% ± 0.19%/min for groups A, B and C, respectively. The mean clearance rate of group A was significantly faster than that of normals ($p < 0.0005$) and group B ($p = 0.028$). In addition, there was a significant difference between groups B and C ($p = 0.015$).

In conclusion, Ga-67 lung scintigraphy is a useful method for the detection of AIPT but Tc-99m-DTPA aerosol scintigraphy offers better results than Ga-67 scintigraphy. Early changes in Tc-99m-DTPA clearance may be observed in patients receiving amiodarone. The kep value in patients with AIPT is noticeably increased with respect to the control group. With its favorable physical properties, low cost, lower radiation burden and its ability to be used as an objective measure for the pulmonary clearance rate, Tc-99m-DTPA aerosol scintigraphy appears to be promising in patients receiving amiodarone therapy.

Key words: amiodarone, Ga-67 scintigraphy, Tc-99m-DTPA radioaerosol scintigraphy

INTRODUCTION

Amiodarone hydrochloride, which is used to treat life-threatening cardiac tachyarrhythmia, has been known to cause many side effects and complications.[1] The most serious complication is amiodarone-induced pulmonary toxicity (AIPT), which can be fatal. AIPT may either arise due to a hypersensitivity reaction, a direct toxic effect of the drug or both of these causes. But neither the clinical findings nor the laboratory tests are specific for the diagnosis of AIPT. In this clinical context, alert monitoring is advised for patients under amiodarone therapy.[2,3] Although, the pulmonary function tests are not specific for AIPT, a decrease in diffusion capacity appears to be the most significant finding.[4] Among the imaging studies, high resolution computed tomography (HRCT) has been reported to play an increasingly important role in assessing drug induced lung disease.[5] Previously, gallium-67 (Ga-67) scintigraphy has also been used and found to be helpful in the detection of AIPT.[6] And the use of

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technetium-99m diethylene triamine penta-acetic acid (DTPA) aerosol inhalation lung scintigraphy has been studied for the evaluation of lung toxicity in patients under amiodarone treatment.[7] However, the clinical value of Tc-99m-DTPA aerosol clearance scintigraphy has not been widely investigated in the literature to our knowledge.

In this study, we aimed to investigate the clinical value of Tc-99m-DTPA aerosol inhalation lung scintigraphy in patients with AIPT and compare the results with those of Ga-67 scintigraphy.

MATERIAL AND METHODS

Study population:

The study group totally included 26 cases which were divided into three groups: group A was composed of 7 patients with a diagnosis of AIPT, group B was composed of 8 patients receiving amiodarone therapy but without AIPT and group C was composed of 11 subjects, who were healthy nonsmokers, as a control group. All subjects were selected from those who had never smoked and without a previous history of lung disease.

Laboratory and imaging studies:

All subjects, except those who were healthy, underwent laboratory investigations including arterial blood gas analysis, pulmonary function test, chest X-ray, HRCT and Ga-67 scintigraphy after giving their informed consent. The diagnosis of AIPT was based on when a new symptom and the presence of an abnormality was noted in three of the above-mentioned five investigations. Tc-99m-DTPA aerosol inhalation lung scintigraphy was performed for all groups. Blood analyses were considered abnormal when arterial hypoxia ($PaO_2 < 80$ mmHg) and hypercapnia ($PaCO_2 > 45$ mmHg) were found. The chest X-ray and HRCT were evaluated for the presence of any parenchymal, interstitial or pleural change suggesting pulmonary involvement of amiodarone. Pulmonary function tests including those of flow-volume loop and diffusion capacity (DLCO) were performed with a computer-based spirograph (SensorMedics 2400, USA), and ATS criteria were used for interpretation. A value below 80% of the predicted value was considered abnormal. Pulmonary toxicity was interpreted taking DLCO as a reference. Decreased PFT was not considered as suggestive of AIPT unless it coexisted with decreased DLCO.

The cumulative dose for amiodarone therapy was also calculated by means of the following formula: daily dose (mg/day) × duration of amiodarone treatment (day) in all patients receiving amiodarone therapy.

Scintigraphic studies:

The stability of Tc-99m-DTPA was more than 96% as judged by thin-layer chromatography. All subjects inhaled 1110 MBq Tc-99m-DTPA (in a 2 m*l* volume) produced by a Venticus II nebulizer delivery system aerolized with oxygen at a flow rate of 9 L/min^{-1}. They inhaled Tc-99m-DTPA aerosol during normal tidal breathing and in the supine position for 3 minutes. The nebulizer delivers a heterodisperse aerosol, 0.8 micron in mass median diameter and with a standard geometric deviation of 1.5. Immediately after the inhalation, dynamic thorax images were obtained in a posterior view with a digital gamma camera. Counts were obtained at 1-minute intervals in a 64 × 64 matrix for a total of 10 minutes. Time activity curves were derived from ROIs drawn over the peripheric regions of the lungs in order to exclude the radioaerosol deposition in the central airways. In this way, the rate of clearance of radioactivity from both lungs was

Table 1 Detailed data of patients

Patient no., sex, age (years)	Cumulative dose (g)	Arterial blood gas	DLCO ± PFT	Ga-67 uptake	Kep value %/min
1/M/58*	72	NL	(+)	(+3), right basal region	1.60
2/M/68*	108	NL	(+)	(+2), diffuse lung uptake	1.98
3/M/54*	36	(+)	(+)	NL	3.43
4/M/68*	36	NL	(+)	(+2), left basal region	3.08
5/F/62*	72	NL	(+)	(+3), left perihilar region	1.38
6/M/64*	21	NL	(+)	NL	1.44
7/M/50*	24	NL	(+)	NL	1.43
8/M/45	12	NL	NL	NL	1.35
9/M/71	6	NL	NL	NL	1.24
10/M/53	12	NL	NL	NL	1.42
11/M/65	18	NL	(+)	NL	0.62
12/F/47	45	NL	NL	ND	0.89
13/F/70	18	NL	NL	NL	1.71
14/F/49	288	NL	(+)	NL	1.97
15/M/49	7	NL	(+)	NL	1.21

F, female; M, male; *, Amiodarone-induced pulmonary toxicity; (+), abnormal; NL, normal; ND, not done

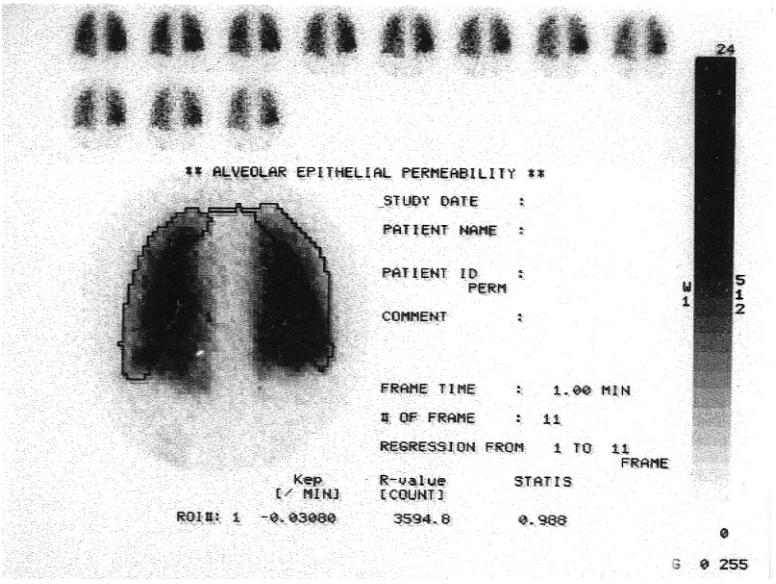

Fig. 1 Tc-99m DTPA aerosol scintigraphy in a 68-year-old patient (patient no. 4) with abnormal DLCO suggestive of amiodarone induced toxicity. Six months after therapy he admitted with a nonproductive cough. The cumulative amiodarone dose that the patient received was 36 g. The clearance rate of Tc-99m DTPA was calculated as 3.08% per min.

calculated as percent per minute. The clearance rate (kep) was expressed in terms of the percentage decrease in Tc-99m-DTPA activity per minute (%/min^{-1}) due to pulmonary epithelial permeability. A Ga-67 scan could be performed in 14 of 15 patients. Anterior and posterior views of the chest were obtained 48 and 72 hr after intravenous injection of 185 MBq (5 mCi) of Ga-67 citrate. The intensity of pulmonary gallium uptake was interpreted qualitatively as diffuse, patchy or focal. Semiquantitative analysis was also performed with a 4-point scale according to liver uptake. 0 = normal; 1 = equivocal; 2 = less than that of liver; 3 = equal to that of liver; 4 = pulmonary activity more intense than liver. Ga-67 accumulation equal to or more than 2 points was regarded as abnormal.

All data are given as the mean ± SD. The Spearman rank correlation test was used for testing the relationship between the kep values and the cumulative dose of amiodarone. The Kruskal-Wallis one-way Anova test and Mann-Whitney U test were used for comparison of kep values for the three groups. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Detailed data are shown in Table 1. Ga-67 scans were abnormal in 4 patients with AIPT where abnormal diffuse (patient no. 2) and focal accumulations (patients: 1, 4 and 5) were noted (Fig. 1). Ga-67 uptake scores were ranging from 2 to 3. In the three remaining patients with AIPT and 8 patients receiving amiodarone therapy the gallium-67 lung scintigraphy result was completely normal.

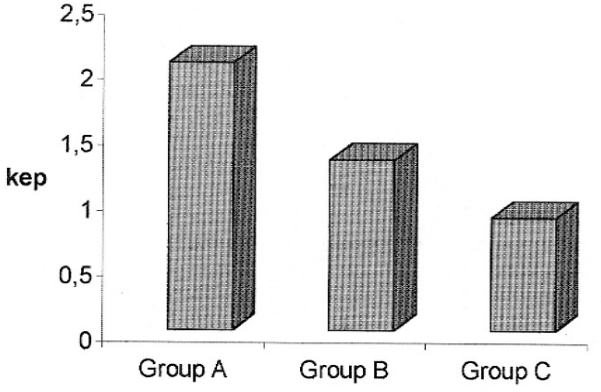

Fig. 2 Representation of the comparative clearance rates (mean kep values) in groups A, B and C.

When Tc-99m-DTPA aerosol studies were reviewed, clearance curves were found to be monoexponential in all patients as well as in the control group. A positive correlation was found ($r = 0.52$, $p < 0.05$) between the kep values for patients and the cumulative dose of amiodarone.

In normal subjects the mean kep value was found to be 0.86% ± 0.19%/min. Corresponding values were 2.04% ± 0.85%/min and 1.30% ± 0.42%/min for group A and group B. Comparative kep values for the three groups are shown in Figure 2. The mean clearance rate for group A was significantly faster than that for normals ($p < 0.0005$) and group B ($p = 0.028$). In addition, there was a significant

difference between groups B and C ($p = 0.015$).

DISCUSSION

It has been reported that pulmonary toxicity may be found in 5–18% of patients who are treated with amiodarone.[8,9] The final diagnosis of amiodarone induced pulmonary toxicity is usually established with a combination of clinical findings, laboratory tests, radiographic studies and histopathologic evaluation. Tissue manifestations of amiodarone toxicity vary and include chronic non-specific interstitial pneumonitis with fibrosis, diffuse alveolar damage and bronchiolitis obliterans with organizing pneumonia. Characteristic foamy macrophages are noted also in BAL specimens. Nevertheless, the presence of foamy macrophages is not indicative of AIPT, because they can also be seen in the majority of patients taking amiodarone who lack evidence of pulmonary toxicity.[8,10]

Ga-67 scintigraphy, which has been widely used in the detection of various inflammatory and neoplastic diseases of the lung, has also been reported to be helpful in AIPT. Although the exact mechanism of uptake is not clearly understood, it is suggested that the lactoferrin affinity of gallium may result in tracer accumulation in areas of pneumonitis. In addition to this, variations in the permeability of cell membranes or blood vessels may cause gallium leakage in this area as well as the tracer accumulation in inflammatory cells.[11] Previously, diffuse, nodular and patchy patterns of positive gallium uptake were described in patients with AIPT.[12] In the current study, four of seven patients with AIPT showed positive Ga-67 accumulation. Gallium uptake was found to indicate a diffuse pattern in one and nodular patterns in three of the cases. But, gallium scintigraphy was normal in 3 patients despite the clinical symptoms and abnormal laboratory data suggesting AIPT. No abnormal gallium uptake was detected in patients without AIPT but receiving amiodarone therapy. In the literature, Terra-Filho and Zhu et al. reported that positive Ga-67 accumulation was noted in 7 of 9 and 18 of 22 patients with AIPT respectively.[6,13] The authors suggested the use of gallium scanning particularly in patients with ambiguous radiographic findings and for the assessment of population at risk.

More recently, Tc-99m-DTPA aerosol scintigraphy has been utilized for the detection of pulmonary epithelial permeability and suggested to be useful in the early stages of diseases involving this barrier. And the rate of clearance of radioaerosol from the lungs has been reported to be a sensitive index for the evaluation of drug and radiation-induced lung injury as well as other infectious or inflammatory changes in lung parenchyma. When inhaled Tc-99m-DTPA particles arrive at the alveolar epithelial surface, they diffuse from the airspace into the vascular space and are finally filtered by the kidneys. Any change or inflammation in the alveola-capillary membrane increases epithelial permeability resulting in faster Tc-99m-DTPA clearance.[14] Amiodarone induced pulmonary toxicity is supposed to result from direct injury related to the intracellular accumulation of phospholipid and T cell-mediated hypersensitivity pneumonitis and is pathologically characterized by interstitial pneumonitis.[15] The risk of AIPT is thought be partly correlated with the total cumulative amiodarone dose.[16] This finding was supported by a statistically significant positive correlation between Tc-99m-DTPA kep values and cumulative doses suggesting a relationship between Tc-99m-DTPA clearance rate and an increasing cumulative dose. Although the correlation coefficient ($r = 0.52$) for the two parameters was not very high, it is thought that the immunologic processes and cumulative dose may also play a role in increasing the clearance rate. The kep value in patients with AIPT had a twofold increase when compared with the control group. In addition to this, statistically increased kep values were also noticed in patients receiving amiodarone therapy but without AIPT. In contrast to our findings, Terra-Filho found no difference in Tc-99m-DTPA lung clearance between patients receiving amiodarone and the normal group. This discrepancy may be explained by the patient characteristics and difference in doses of amiodarone therapy in both clinical series. In addition, several studies indicating that phospholipid changes may occur in tissue specimens from patients without evidence of toxicity have also been reported.[17,18] For this reason, early alterations in Tc-99m-DTPA clearance may be observed in patients receiving amiodarone before clinical pulmonary toxicity. These assumptions are also supported by the study of Uğur et al. The authors found increased kep values in all patients receiving bleomycin and suggested the use of Tc-99m-DTPA aerosol study for monitoring the functional status of the lung epithelial permeability.[19] However, there are no clear data on the timing of the imaging studies in the evaluation of AIPT. This is because the occurrence of AIPT is not predictable and may occur even without clinical toxicity findings. Therefore, we suggest that a baseline Tc-99m-DTPA aerosol study is useful in patients receiving amiodarone and may assist in the long-term assessment of possible pulmonary toxicity.

In conclusion, Ga-67 scintigraphy and Tc-99m-DTPA aerosol scintigraphy are found to be useful in the identification of patients with AIPT. The simplicity of the procedure, physical characteristics, low-cost and lower radiation exposure than Ga-67 scintigraphy are the advantages of Tc-99m-DTPA aerosol scintigraphy. Moreover, Tc-99m-DTPA aerosol scintigraphy also provides an objective assessment of lung epithelial permeability in clinical follow-up patients receiving amiodarone therapy. However, further studies in large series are warranted for the assessment of Tc-99m-DTPA clearance rates in the prediction of patients under the risk of pulmonary complications of amiodarone.

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