Acute Paraquat Intoxication*
Using Nuclear Pulmonary Studies to Predict Patient Outcome

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Study objectives: Paraquat, a widely used herbicide, has been shown to cause severe and often fatal pulmonary fibrosis in humans and laboratory animals. Although paraquat is known to be directly cytotoxic to lung parenchyma, changes in routine lung scintigraphy results after acute paraquat intoxication have not been reported. The objective of this project was to investigate changes in lung ventilation (LV) and alveolar permeability (AP) in patients with paraquat intoxication, using $^{99m}$Tc diethylenetriamine pentaacetate (DTPA) radioaerosol lung scintigraphy.

Design: Prospective, blinded study.

Setting: Nuclear medicine and toxicology departments in two university-affiliated teaching hospitals.

Patients or participants: Thirteen patients with acute paraquat intoxication were included in this study. Ten volunteers without acute paraquat intoxication were studied for comparison.

Measurements and results: $^{99m}$Tc DTPA aerosol inhalation and $^{99m}$Tc macroaggregated albumin (MAA) perfusion lung scintigraphies were performed to determine LV, AP, and lung perfusion (LP). Five of the 13 patients (38%) had significant LV abnormalities; 3 of these 5 patients also showed abnormal LP. Of the 13 patients, 4 patients (31%) showed normal AP and survived. The remaining 9 patients (69%) showed abnormal AP and died. The mean values for AP were statistically different ($p < 0.01$) between survivor (0.72 ± 0.16%) and nonsurvivor (1.52 ± 0.40%) groups. Data from the normal volunteers and survival patients showed a $^{99m}$Tc clearance slope < 1.00%. Data from patients who died showed a clearance slope > 1.00%.

Conclusion: These results indicate that AP, measured by $^{99m}$Tc DTPA aerosol inhalation lung scintigraphy, may help predict outcome in patients with paraquat intoxication.

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Key words: alveolar permeability; lung perfusion; lung ventilation; paraquat intoxication

Abbreviations: AP = alveolar permeability; DTPA = diethylenetriamine pentaacetate; LP = lung perfusion; LV = lung ventilation; MAA = macroaggregated albumin; ROI = region of interest

Reports by all poison centers from 1985 to 1990 indicate the occurrence of 27,087 cases of herbicide intoxication in the United States, of which 1,317 cases (4.9%) were paraquat related (an average of approximately 263 cases per year). Paraquat poisoning accounted for a disproportionately high mortality rate in this group: 13 of 24 deaths (54%) resulted from paraquat poisoning.1 From 1971 to 1985, 231 paraquat-related cases (an average of approximately 14 cases per year) were reported to the Worker Health and Safety Branch, California Department of Food and Agriculture.2 The peak blood level of paraquat normally appears 2 h after oral intake. The blood level of paraquat then decreases rapidly, stabilizing for 15 to 20 h. During this period, paraquat progresses from blood into tissues and then is excreted by the kidney. The peak level of paraquat in the kidney occurs at 3 h after intake. If renal function is normal, 80 to 90% of the paraquat could be excreted from urine at 6 h after intake and 100% at 24 h after intake.3–5 Paraquat causes irre-
versatile progressive pulmonary fibrosis and obliteration of alveoli in the human lungs. The number of alveoli in paraquat-intoxicated patients is reduced in comparison to controls. The paraquat-affected lung shows alveolar collapse and infiltration of inflammatory cells into alveolar airspace. Reduced lung volume and lung compliance result in hypoxemia and respiratory failure. Therefore, respiratory failure due to direct cytotoxic action on lung parenchyma may be the major cause of death in patients with acute paraquat intoxication.

In recent years, there has been an increase in the use of 99mTc diethylenetriamine pentaacetic acid (DTPA) radioaerosols for clinical investigations. Aerosols have replaced radioactive gases such as 81mKr and 133Xe in some centers. 99mTc DTPA radioaerosols generated by a jet nebulizer are inexpensive, readily available, and have high scintigraphic quality. The radiation hazard to staff per 30 consecutive frames of 1 min each in a 64 matrix with large-field computerized gamma camera for the posterior view of the lungs. The data were acquired as a series of 200,000 counts by normal tidal breathing. Data were collected for 30 min by means of a large-field computerized gamma camera for the posterior view of the lungs. The data were acquired as a series of 30 consecutive frames of 1 min each in a 64 × 64 matrix with word mode. After background correction, the first image in the series was selected as the LV image. Two independent observers judged the LV images according to established criteria, which included the presence or absence of inhomogeneous tracer.

**Materials and Methods**

Thirteen patients (5 women and 8 men; age, 16 to 66 years old) with acute paraquat intoxication from oral intake due to intended suicide or accident were admitted to our hospital (Table 1). The duration from exposure to admission was 0.5 to 2 h. Within 2 to 4 h after admission, the blood and urine levels of paraquat were measured. Then, 99mTc DTPA aerosol inhalation and 99mTc MAA perfusion lung scintigraphies were performed to determine LV/AP and lung perfusion (LP). The duration of hospitalization was from 1 to 17 days. Survival was defined as alive at the time of discharge (four patients). The rest (nine patients) died before day 17. Ten volunteers without acute paraquat poisoning (3 women and 7 men; age, 26 to 66 years old) were studied for comparison (Table 2). All of the control subjects’ chest radiograph findings were normal. None of the control subjects or test patients had a history of smoking.

99mTc was chelated to DTPA (Daichi Radioisotope; Tokyo, Japan) by introducing 50 mCi of 99mTcO4 into a vial containing 20 mg DTPA and 2.5 mg stannous chloride (SnCl2). 99mTc DTPA aerosol was prepared within 1 h before use. 99mTc DTPA aerosol was generated from the aerosol delivery unit (AeroVent model AV-400; Medi/Nuclear Corporation; Baldwin Park, CA) containing 20 mCi 99mTc DTPA in 2 mL saline solution. Radioaerosol droplet size was measured by an inertial impactor (model PC-2; CA Measurement, Inc; Sierra Madre, CA). The mass median aerodynamic diameter of the 99mTc DTPA aerosol (Medi/Nuclear) was <1 μm, with an oxygen flow rate of approximately 10 L/min. Because good patient compliance and ventilation of the gamma camera room are important factors in minimizing radiation dose, we performed each radioaerosol study in a ventilated room and asked the patients to practice the following procedure to help reduce airborne contamination from them. All subjects were studied while in the supine position; the subjects inhaled normally from the aerosol delivery unit for 2 min until the total radioactivity was >200,000 counts by normal tidal breathing. Data were collected for 30 min by means of a large-field computerized gamma camera for the posterior view of the lungs. The data were acquired as a series of 30 consecutive frames of 1 min each in a 64 × 64 matrix with word mode. After background correction, the first image in the series was selected as the LV image. Two independent observers judged the LV images according to established criteria, which included the presence or absence of inhomogeneous tracer.
Table 2—Data of Normal Control Subjects*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>LV</th>
<th>LP</th>
<th>AP, %</th>
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<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
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<td>Normal</td>
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<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>Normal</td>
<td>Normal</td>
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<td>F</td>
<td>Normal</td>
<td>Normal</td>
<td>0.64</td>
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<tr>
<td>4</td>
<td>32</td>
<td>M</td>
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<td>Normal</td>
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</tr>
<tr>
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<td>52</td>
<td>M</td>
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<td>M</td>
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<td>Normal</td>
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</tr>
<tr>
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<td>Normal</td>
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<tr>
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<td>48</td>
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<tr>
<td>10</td>
<td>37</td>
<td>M</td>
<td>Normal</td>
<td>Normal</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*See legend to Table 1 for expansion of abbreviations.

distribution between the central and peripheral lung, inverted base-to-apex gradient tracer distribution, and local segmental/subsegmental hypventilation defects. The summation of the series of 30 images was displayed. One region of interest (ROI) was manually created around the total right lung following the 20% maximum activity contour. After radioactivity was corrected for radionuclide decay and background correction by another ROI over the right shoulder, the time-activity curve was individually generated over the total right lung. An exponential line of best fit was calculated for the ROI. The negative slope of this regression line was designated as the washout rate and was expressed in terms of percentage decrease of radioactivity per minute. The reason for the preference of the right lung for analysis of radioactivity clearance was to avoid background radioactivity from the stomach. After 99mTc DTPA aerosol inhalation lung imaging, all subjects underwent 99mTc MAA perfusion lung imaging in the supine position. 99mTc MAA aerosol ventilation image (left, A, posterior view) reveals a hypoventilation area in the right side of the upper lung (arrow); the 99mTc MAA perfusion image (right, B, posterior view) shows matched perfusion defects in the same area (arrow).

Figure 1. In a 32-year-old patient with paraquat intoxication (nonsurviving patient 7 in Table 1), the 99mTc DTPA radioaerosol ventilation image (left, A, posterior view) reveals a hypoventilation area in the right side of the upper lung (arrow); the 99mTc MAA perfusion image (right, B, posterior view) shows matched perfusion defects in the same area (arrow).

Figure 2. In a 46-year-old patient with paraquat intoxication (nonsurviving patient 13 in Table 1), the 99mTc DTPA radioaerosol ventilation image (left, A, posterior view) reveals inhomogeneous tracer distribution and multiple hypventilation areas in both lungs; the 99mTc MAA perfusion image (right, B, posterior view) reveals no significant perfusion abnormalities.

Results

The detailed data are listed in Table 1. Of the 13 patients, only 4 patients were discharged alive. The other nine patients died. The blood levels of paraquat for all 13 patients ranged from 0.1 to 28.1 (6.5 ± 9.7) μg/mL; 0.1 to 2.6 (0.9 ± 1.2) μg/mL, and 0.1 to 28.1 (9.0 ± 10.8) μg/mL for survivors and nonsurvivors, respectively (p > 0.05 by Mann-Whitney U test). The urine levels of paraquat for all 13 patients ranged from 2.4 to 522.5 (144.4 ± 188.9) μg/mL; 2.4 to 45.4 (15.7 ± 20.0) μg/mL, and 5.3 to 522.5 (201.6 ± 203.6) μg/mL for survivors and nonsurvivors, respectively (p > 0.05 by Mann-Whitney U test).

Of the 13 patients, 5 patients had significant LV abnormalities (38%). Three of the five patients showed matched LP abnormalities (Fig 1), and the other two patients revealed normal LP (reverse mismatch; Fig 2). Additionally, all four surviving patients showed both normal LV and normal LP (Fig 3). Four of the 13 patients (31%) had normal AP and survived. However, the remaining nine patients (69%) showed abnormal AP and died. The mean values for AP are statistically different (p < 0.01 by Mann-Whitney U test) between survivor (0.72 ± 0.16%) and nonsurvivor (1.52 ± 0.40%) groups. Data from the normal volunteers and survivors showed a 99mTc clearance slope < 1.00% (0.53 to 0.98%); and data from the nonsurvivors showed a clearance slope > 1.00% (1.03 to 2.07%). In addition, moderate correlations were found between paraquat blood level and AP value (R = 0.61; Fig 4) and between urine level and AP value (R = 0.50; Fig 5).

Discussion

The lung parenchyma is essentially a three-compartment structure consisting of the alveolar space, the vascular space, and the interstitium. The integrity of these compartments is fundamental to the maintenance of normal gas exchange. Small aerosols can move across these compartments via transcellular and intercellular routes. The 99mTc DTPA radioaerosol inhalation lung scan is a sensitive
marker for the changes in AP. $^{99m}$Tc DTPA is deposited in the lining of the pulmonary epithelial surface and then passes through the barrier. AP abnormalities can be detected with this technique. The early occurrence of AP abnormalities appears to be a very sensitive index of pulmonary damage.

Smoking significantly increases lung clearance of $^{99m}$Tc DTPA radioaerosols. In this study, patients with acute paraquat intoxication and normal volunteers with a smoking history were excluded. The mean values for AP were statistically different ($p < 0.01$ by Mann-Whitney U test) between survivor (0.72 ± 0.16%) and nonsurvivor (1.52 ± 0.40%) groups. Data from normal volunteers and survivors showed a clearance slope $< 1.00\%$. Therefore, $^{99m}$Tc DTPA lung clearance rate (if the cutoff is 1.00%) may be proven to be a good predictor of outcome in acute paraquat intoxication. However, the separation between survivor (patient 4 [0.95%]) and nonsurvivors (patients 5 [1.03%] and 6 [1.06%]) was not wide, and there may be some overlap (Table 1).

Lungs from patients and animals who died after ingesting paraquat have been studied histopathologically. The predominant change is the remodeling of alveolar structure caused by infiltration of inflammatory cells and erythrocytes into both the interstitium and alveolar airspaces, detachment of alveolar epithelial cells from the basement membrane, and total obliteration of alveoli. These findings may explain why enhanced AP and abnormal LV occur in patients with acute paraquat intoxication.

The obliteration of alveoli and reduction in lung volume appear to be related to the paraquat levels in blood. The correlation between paraquat levels in blood and AP is shown in Figure 4.

![Figure 3](image_url)

**Figure 3.** In a 24-year-old patient with paraquat intoxication (surviving patient 3 in Table 1), the $^{99m}$Tc DTPA radioaerosol ventilation image (left, A, posterior view) is normal except for significant stomach activity (arrow); the $^{99m}$Tc MAA perfusion image (right, B, posterior view) reveals normal perfusion in both lungs.

![Figure 4](image_url)

**Figure 4.** Correlation between paraquat levels in blood and AP.
volume may result in regional alveolar hypoxia followed by reflex hypoxic pulmonary vasoconstriction.\textsuperscript{31,32} This was considered to be the cause of the matched LV and LP defects observed in patients 7, 9, and 11 (Table 1). However, a number of investigations have demonstrated the “reverse mismatch” phenomenon. The most frequent causes of this phenomenon are pneumonia, collapse and atelectasis, pleural effusions, chronic obstructive airway disease, metabolic alkalosis, endobronchial obstruction, pulmonary hypertension, and positive-pressure ventilatory support.\textsuperscript{33} Reverse mismatch associated with paraquat intoxication was found in patients 5 and 13 (Table 1). A possible factor in the failure of hypoxic vasoconstriction in patients with acute paraquat intoxication is the local release of inflammatory mediators with vasodilatory properties.\textsuperscript{31,32}

Because most of our patients had normal renal function (blood levels of BUN, 8 to 25 mg/dL; creatinine, 0.6 to 1.5 mg/mL; Table 1), the discordance between blood and urine paraquat levels was due to individually variable excretion rates of paraquat from blood to urine according to paraquat pharmacokinetics.\textsuperscript{3–5} Previous reports\textsuperscript{4,34} have suggested that measurement of blood or urine paraquat concentration is useful in predicting the outcome of poisoning. Proudfoot et al\textsuperscript{4} found that patients whose blood concentrations are not $> 20 \ \mu g/mL$ at 4 h are likely to survive. In our study, the blood levels of paraquat between survivors (0.9 \pm 1.2 \ \mu g/mL) and nonsurvivors (9.0 \pm 10.8 \ \mu g/mL) were not significantly different ($p > 0.05$). However, the blood levels in all of four survivors were $< 20 \ \mu g/mL$, whereas the levels in two nonsurvivors (patients 7 and 13) were $> 20 \ \mu g/mL$. Scherrmann et al\textsuperscript{34} found that in all 30 patients with paraquat intoxication studied, those whose urine paraquat concentration was $> 10 \ \mu g/mL$ survived. In our study, the variations in urine levels between survivors ($15.7 \pm 20.0 \ \mu g/mL$) and nonsurvivors ($201.6 \pm 203.6 \ \mu g/mL$) were also not significantly different ($p > 0.05$). However, the urine levels were $< 10 \ \mu g/mL$ in three of four survivors (75%), but only in one of nine nonsurvivors (11%).

In a review of the literature, increased lung clearance of $^{99m}$Tc DTPA has also been reported after inhalation of various substances such as tobacco, crack cocaine, marijuana, inhalants (such as glue), heroin, or amphetamine.\textsuperscript{27,35–37} Therefore, we em-
phrased (as many other nuclear medicine investigations have indicated) that the technique—although nonspecific—is rapid, easy to perform, and extremely sensitive in the detection of lung disease in certain circumstances. We conclude that \(^{99m}\)Tc DTPA radioaerosol inhalation lung scintigraphies may provide a sensitive determination of acute lung damage and may help to predict the outcome in patients with acute paraquat intoxication.

References

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Clinical Investigations