Clinical Evaluation of a New ^{99m}Tc-MAA Kit for Lung Scanning

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Lung scanning has been recognized as a clinically useful technique for portraying macroscopic pulmonary perfusion defects since it was first reported by Wagner in 1964 (*1*). A number of radiopharmaceuticals have been proposed to assess pulmonary perfusion. Although ^{131}I imposes many limitations as a radiotagging agent, the use of iodinated macroaggregated albumin (I-MAA) has received wide acceptance as the agent of choice. The desirability of ^{99m}Tc as a scanning agent, especially for static imaging systems, has long been recognized and leads to the ultimate development of ^{99m}Tc-tagged human albumin microspheres (Tc-HAM) (*2*). Technetium-99m-labeled macroaggregated albumin (Tc-MAA), although desirable, has not been exploited for lung scanning because of the technical requirements encountered during its preparation (*3*).

Recently, a lyophilized macroaggregated albumin kit (Macrotec) for preparing Tc-MAA has undergone field trials by E.R. Squibb & Sons. Preparation of Tc-MAA from this kit yields a stable product which on standing may be used without resuspension and rewashing the tagged particles to remove sequestered technetium. Preparation and clinical evaluation of the Macrotec kit was undertaken in our laboratories from July 1972 to February 1973 and is the subject of this report.

Materials and Method

Macrotec (^{99m}Tc-Sn-MAA) is a lyophilized, sterile preparation containing 1.5 mg denatured human serum albumin, 0.13 mg stannous chloride ($SnCl_2 \cdot 2H_2O$) and 10 mg normal serum albumin in each vial. The contents are reconstituted with 1—3 ml of eluate containing ^{99m}Tc-pertechnetate from a molybdenum-technetium generator. For our investigation we reconstituted with 3 ml fixed volume of eluate containing 20 mCi ^{99m}Tc-pertechnetate and gently swirled the vial to prevent particle fracture. By establishing a fixed volume containing 20 mCi of eluate, we were able to control and reproduce the agent by maintaining the specific activity at 0.075 mg/mCi of serum albumin for each injected dose. Administering less than 0.025 mg/mCi of serum albumin produced lung images that were mottled in appearance due to the inadequate number of particles in the injected volume.

Size specifications require that at least 90% of the particles must range between 10 and 100 microns with none over 150 microns. In our investigation, particle size and concentration were measured by using a phase microscope and standard hemocytometer techniques (Fig. 1). Paper chromatography of the final preparation was carried out to determine the percent labeling of ^{99m}Tc to the MAA particles. The destructive ascending paper chromatography technique described by Gutowski (*4*) using Whatman No. 1 chromatographic paper in an 85% methanol-water interface was employed (Fig. 2). Before submission to destructive chroma-

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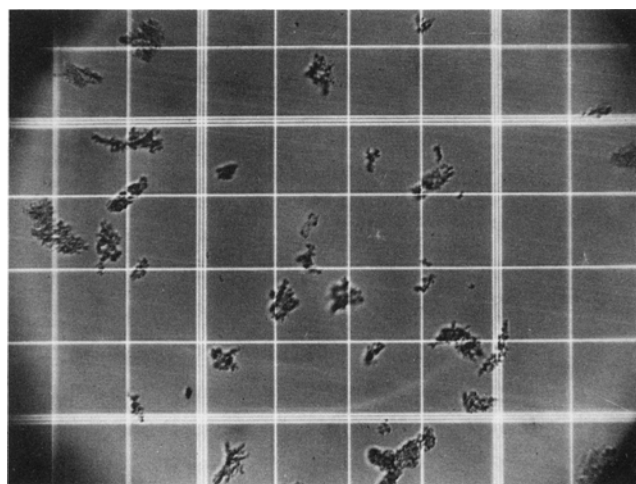

FIG. 1. Photomicrograph of Tc-MAA particles in typical field. Small squares are 40 x 40 microns.

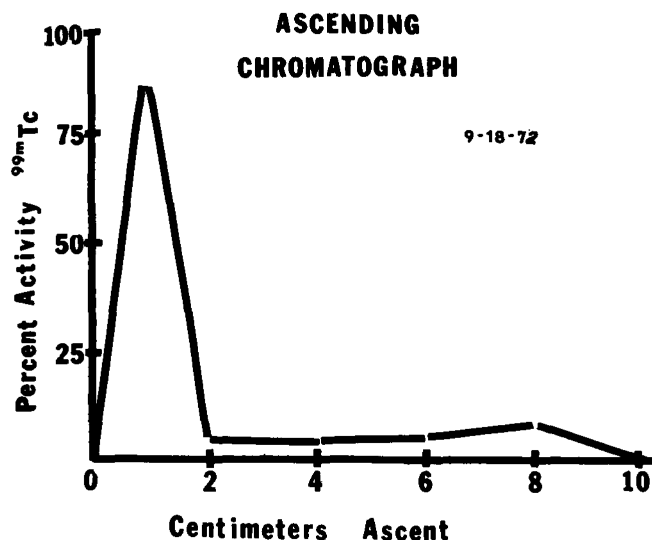

FIG. 2. Plotted results of destructive analysis from ascending chromatograph. Origin activity confirmed 88% technetium particle tagging.

tography, the chromatograph was placed in a cellophane bag to prevent contamination and then placed on our scintillation camera detector head where a scintiphoto was made. The resulting picture permitted a qualitative assessment of technetium to particle binding (Fig. 3).

One hundred subjects presented to the laboratory for routine evaluation of pulmonary perfusion were administered 3 mCi of the Tc-MAA intravenously without premedication. Three of these patients were selected to be control subjects for determination of clearance time for Tc-MAA from the lungs, organ distribution, and excretion. External port counts were taken over the lungs and liver during the 72-hr period postinjection. Urinary excretion was measured for radioactivity with 24-hr collection specimens for 3 days. In addition, blood samples were taken periodically for 24 hr following injection for measurement of radioactivity. Temperature, pulse, and respiration of all subjects studied were noted for 24 hr after administration of the scan agent. Eight-view lung scans, including anterior, posterior, left and right laterals, with anterior and posterior oblique views of both lungs were obtained with a scintillation camera. Total accumulated activity per view averaged 500,000 counts and required approximately 1 min with a 3-mCi dose. Selected interesting cases were restudied the following day with either I-MAA or Tc-HAM for comparative lung scan quality using the identical scanning projections.

Results

Particle preparation. Control studies were performed on each batch of Tc-MAA produced during the course of this study. Particle size was assessed with phase microscopy which showed that particles ranged in size from 10 to 120 microns. The majority of particles produced varied between 20 and 80 microns. Particle configuration was usually in a strand shape (Fig. 1). Particle concentration per cubic centimeter of Tc-MAA remained reasonably constant with the establishment of a standard method for production as outlined previously. The concentration of particles ranged between 350,000 and 525,000 particles/cc with an average concentration of 400,000 particles/cc. Since approximately 0.5 cc of the preparation was required for a 3-mCi dose, the average number of particles per injection was 200,000.

Percentage tagging of the particles with technetium-pertechnetate varied between 60 and 95% as determined by paper chromatography (Fig. 2). The less efficient tagging was noted in earlier preparations of Tc-MAA. Batches of material obtained since January 1973 have produced a more uniform particle with greater tagging efficiency. The overall average of tagging during our investigation was 80%. Chromatographic analysis is time consuming and led us to perform scintiphotos of the chromatograph without submitting the study to destructive methods. It was soon learned that visual inspection of the scintiphoto often proved adequate for the identification of poor tagging. Concentration of any magnitude in the Macrotec column, identifiable as technetium-pertechnetate by the marker column, usually indicated tagging efficiencies of less than 70%. Using this method has made it possible to carry out chromatographic analysis in approximately 1/2 hr.

Metabolic studies. Three subjects in the present series were submitted to stationary probe counts over the lung and liver periodically during the first

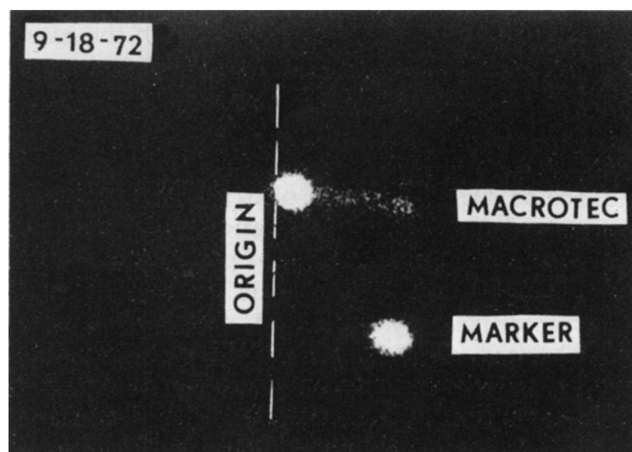

FIG. 3. Scintiphoto of same chromatograph plotted in Fig. 2. Marker shows ascent of technetium-pertechnetate. Note tail on Macrotec column which represents 12% of technetium unbound to MAA.

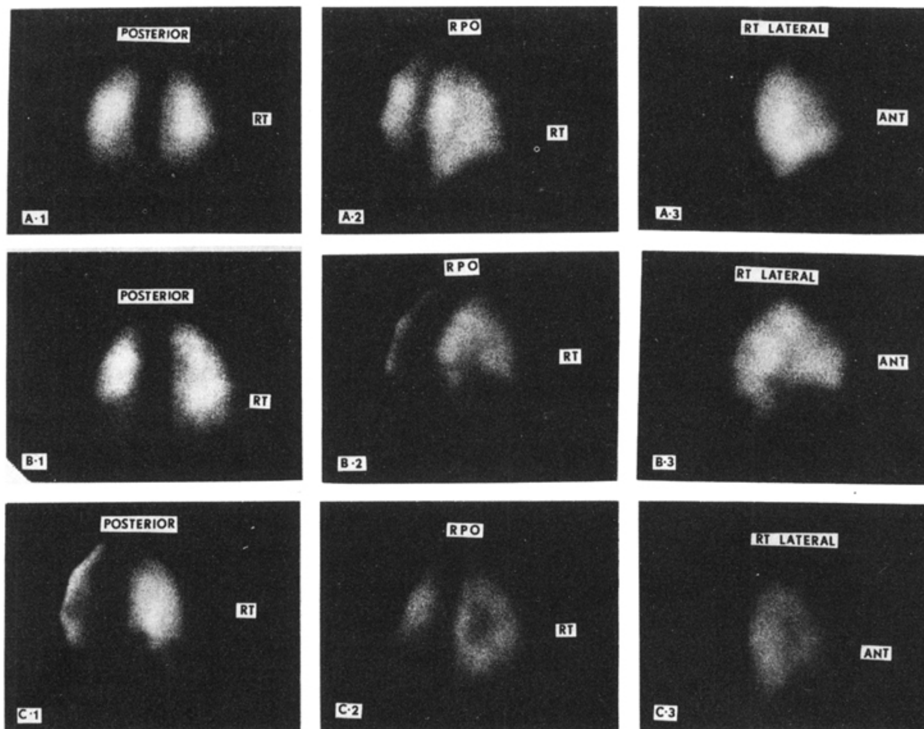

FIG. 4. Perfusion imaging with Tc-MAA in posterior, right posterior oblique, and right lateral projections, (A) Views of normal right lung. (B) Pulmonary embolus at right anterior base. (C) Chronic obstructive pulmonary disease. Note uneven and mixed perfusion pattern with prominent pulmonary hilar defect seen in RPO projection.

24 hr postinjection. The half-time disappearance of activity over the lung port varied between 3 and 5 hr. Liver activity rose to a maximum at 6 hr postinjection with a half-time disappearance of 16 hr after maximum liver accumulation. Serial studies of blood activity demonstrated no measurable activity 10 min postinjection. Two percent of the total administered dose appeared at 4 hr and less than 1% of the total activity was noted at 24 hr. Urinary excretion accounted for 25% of the total administered dose at 24 hr, and 40% of the total administered dose by 72 hr. Fecal excretion of activity was not determined.

Scan interpretation. One hundred cases were accumulated during the course of the present study. Retrospective analysis of charts was carried out for all studies not regarded to be normal. Of the cases studied, 42 were interpreted as normal. Subsequent clinical interpretation suggested that 23 studies correlated with the impression of pulmonary embolus. Twenty-eight additional studies had other evidence to suggest chronic obstructive pulmonary disease and two had confirmation of significant pleural effusions. Three cases of pulmonary tumor were verified, and two patients with pneumonia were recognized by abnormal perfusion studies with x-ray and laboratory confirmation of pneumonia.

All studies were performed with the scintillation camera accumulating at least 500,000 counts per picture. Scan time for each view was approximately 1 min which resulted in uniform and even perfusion throughout normal lung tissue. Eight-view lung scans as described previously gave optimal inspection of the lung bases with assurance that perfusion defects could be recognized easily. This technique has been helpful in enabling the interpreter to look en-face at defects in the pulmonary field (Fig. 4). Defects in the midlung field, especially with the lateral and oblique projections, were felt to correlate with bronchovascular structures at the pulmonary hilus. Indentations due to ribs were seen in a few studies and lobar fissures frequently appeared as normal pulmonary landmarks.

A few selected cases were serially restudied with I-MAA using the scintillation camera. Fine detail, as mentioned above, was not seen with this agent, and time per scan view was 10—12 min. Uneven and irregular perfusion distribution as correlated with obstructive pulmonary disease was visible much earlier with Tc-MAA. Serial studies employing Tc-HAM detailed perfusion defects identical to those visualized with Tc-MAA. It was noted, however, that scans performed with Tc-MAA and regarded to be normal often were found to have an irregular and mottled appearance when restudied with Tc-HAM. These cases did not present other clinical evidence to support the diagnosis of chronic obstructive pulmonary disease. We conclude that the larger number of particles employed with Tc-MAA may give a more accurate assessment of subtle and early changes in pulmonary perfusion.

Conclusion

Our experience with Tc-MAA has been brief but sufficient to suggest a number of advantages over

the currently available lung perfusion agents. The present kit preparation of Tc-MAA is very stable and does not require complicated procedures for preparation. Stability of the resulting tagged particle is good. There is no necessity for resuspending particles before injection or washing particles to remove free technetium from the product. The efficiency of particle labeling is acceptably high which minimizes unwanted circulatory activity in the field of interest. Interpretation of the Tc-MAA scan is reliable and predictable, making assessment of early obstructive pulmonary changes more certain. The favorable photon yield from technetium and activity available at the present dose of Tc-MAA make multiple views possible with more accurate evaluation of basilar pulmonary defects.

References

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