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PREPARATION OF A ^{99m}Tc-Sn-MAA KIT FOR USE IN NUCLEAR MEDICINE

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A method of preparation of an MAA kit which has a high labeling efficiency with ^{99m}Tc, a consistent particle size, and stability with time is described. This kit can be prepared in varying amounts and should allow most nuclear medicine departments to take advantage of the desirable physical characteristics of ^{99m}Tc.

Since first suggested in 1964 (*1*), labeled macroaggregated albumin (MAA) has become widely used as a lung perfusion scanning agent. Owing to its availability and superior decay characteristics, generator-produced ^{99m}Tc has been increasingly used to label MAA. Methods of preparation of ^{99m}Tc-MAA include aggregation of ^{99m}Tc-labeled albumin (*2–4*) and the simultaneous aggregation of albumin and ^{99m}Tc-labeled sulfur colloid (*5*). Both of these methods require considerable daily preparation time and labeling efficiency and particle size may be quite variable. These procedures also require considerable manipulation of the "hot" radiopharmaceutical and hence an increase in personnel radiation exposure. Because of these shortcomings and the requirement for experienced personnel to prepare the ^{99m}Tc-MAA, many nuclear medicine laboratories have been forced to use ^{131}I-MAA in spite of its less desirable radiation characteristics. Recently, the preparation of ^{99m}Tc-MAA kits has been reported where particle preparation takes place before the introduction of the radionuclide (*6–9*). However, these kits also require some manipulation or have been shown to yield variable tagging efficiencies or occasionally to give liver uptake.

This paper describes a method of preparation of an MAA kit which has a high labeling efficiency in which particle size can be carefully controlled and which is stable for at least 2 months when stored at 4°C. Labeling requires only the addition of pertechnetate with no further manipulation.

METHODS

The preparation of the MAA kit is based upon the method of Subramanian (*9*). However, certain changes in procedure were found to be necessary to ensure a uniform particle size without the need for aspiration and a consistently high tagging efficiency.

Into a sterile 50-ml vial containing a magnetic stirring bar is added with Millipore filtration (0.22 micron):

1. 5.0 ml of a solution containing 100 mg/ml of sodium acetate and 10 mg/ml of human serum albumin.
2. 19.0 ml of sterile water for injection.
3. 1.0 ml of a solution containing 5.0 mg/ml of stannous chloride in 1 *N* HCl.

The pH at this point is approximately 5.5. The vial and contents are then heated in a water bath at 80°C for 8 min. The temperature should be maintained as closely as possible to 80°C. The solution is continually mixed during this time with a water-powered magnetic stirrer. After heating, the vial and contents are cooled and the particle size of the aggregates is determined using a hemocytometer. One milliliter aliquots of the MAA suspension are then dispensed into sterile 7-ml vacutainers (Beckton, Dickinson and Co.). The vacutainers are centrifuged at 2,800 rpm for 10 min and the supernatant is removed. The particles are resuspended in an equivalent volume of nitrogen-purged saline for injection and the MAA kits are stored at 4°C. Before use, quality control procedures including testing for particle number and size distribution, labeling efficiency, sterility, and apyrogenicity are done on samples of each batch of the kit.

Labeling of the MAA kit is accomplished by adding sufficient $^{99m}TcO_4^-$ in saline to allow the injection of 1×10^5 to 2×10^6 particles. Up to 4 ml of $^{99m}TcO_4^-$ in saline may be added. To achieve maximum tagging efficiency, the vial is rotated at about 15 rpm for 10 min on a commercial rotator behind lead shielding.

The concentration of radioactivity in the lung, liver, and blood of male adult mice, sacrificed 10 min, 1 hr, 3 hr, 6 hr, 12 hr, and 18 hr after tail vein injection of kit ^{99m}Tc-MAA was determined. The

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mean of the results from six animals at each time interval was calculated.

RESULTS

A total of 12 batches of macroaggregated albumin kits have been prepared by this method. The particle size range has been consistently 10–50 microns with a mean particle size of 30 microns. We find it unnecessary to aspirate the particles after preparation and the particle number and size distribution is very reproducible from lot to lot. Tagging efficiency with ^{99m}Tc as determined by ascending thin-layer chromatography in normal butanol has been found to be greater than 95% in all cases.

Studies into the stability of the MAA kit indicate that when stored at 4°C, either resuspended in nitrogen-purged saline or left dry, the particles retain their integrity and labeling efficiency for at least 2 months. Trapping efficiency of particles stored for 2 months is greater than 95% in the lungs of mice. Storage of the kit in a freezer or freeze-dried results in breakdown of the particles although the tagging efficiency is retained.

Tissue distribution studies in mice were conducted up to 18 hr after tail-vein injection with ^{99m}Tc-MAA. The results are shown in Table 1. The ^{99m}Tc-MAA had an initial mean concentration of 97.3% in the lungs, 1.6% in the liver, and 1.4% in the blood. The clearance half-time of the ^{99m}Tc label from the lungs was 5.4 hr. Forty-eight hours after administration, a mean of 1% of the activity remained in the lungs while 8% remained in the liver.

Over 75 human lung scans have been done using this ^{99m}Tc-MAA kit. All have been of good quality. Counting rates over the liver, before and after scanning, have been compared with the counting rate over the lungs. Before scanning, the counting rate over the liver was found to be 3.5 ± 1.9% of that over the lung while, after scanning, it was found to be 4.2 ± 1.7%. In no instance has liver activity interfered with interpretation of the pulmonary scan.

TABLE 1. TISSUE DISTRIBUTION OF KIT ^{99m}Tc-MAA IN MICE

Time after administration	Percent of administered dose*		
	Lungs	Liver	Blood†
10 min	97.3 ± 4.1	1.6 ± 0.1	0.7 ± 0.1
1 hr	79.6 ± 3.6	1.8 ± 0.3	0.9 ± 0.1
3 hr	61.6 ± 7.2	5.5 ± 2.3	1.8 ± 0.5
6 hr	39.0 ± 5.8	7.3 ± 0.4	0.7 ± 0.1
12 hr	22.7 ± 2.2	7.0 ± 1.3	0.4 ± 0.1
18 hr	8.8 ± 0.4	16.9 ± 1.5	1.9 ± 0.3

* Mean of six animals ± standard error of the mean.
† Per milliliter of blood.

DISCUSSION

This MAA kit has been found to give excellent lung perfusion scans while entailing a minimum of preparation time. Particles are consistently between 10 and 50 microns and aspiration of the final product is unnecessary. The tagging efficiency of the preparation has consistently been above 95%.

Removal of the supernatant and resuspension of the MAA in nitrogen-purged saline was found necessary to eliminate the occasional significant uptake by the liver. However, attempts to label the supernatant with ^{99m}Tc have been unsuccessful. An explanation may be that the pertechnetate ion is reduced by stannous ions attached to the MAA particles and then becomes labeled to colloidal particles in the supernatant.

The monthly preparation of this kit takes approximately 2 hr. The kit is stable for at least 2 months. By doubling the amount of reagents used, up to 50 individual kits can be prepared at one time. Daily tagging time is a few minutes and as many as ten lung scans can be obtained with one kit. Because of the speed of preparation, we are now able to check routinely radiochemical purity as well as particle size before the preparation is injected.

The introduction of "instant" MAA kits should enable most nuclear medicine departments to take advantage of the desirable physical characteristics of ^{99m}Tc so that lower patient radiation doses and better quality lung scans can be obtained.

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