^{99m}Tc-IRON HYDROXIDE AGGREGATES FOR LUNG SCANNING

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The most widely used lung-scanning material—^{131}I-macroaggregated albumin—suffers from several disadvantages: (1) the thyroid gland must be blocked, (2) the photon flux is low from activities (300 μCi) which deliver an acceptable radiation dose to the lung and (3) the scanning times are therefore long. These disadvantages have led to the introduction of lung-scanning agents labeled with short-lived radionuclides. The ^{113m}In-iron hydroxide aggregates introduced by Stern *et al* (*1*) produce excellent scans although the half-life (104 min) is inconveniently short. Preparation of the ^{99m}Tc-macroaggregated albumin particles described by Harper *et al* (*2*) is at present too complex and time consuming for routine practical use.

Nosslin has developed a method for preparing iron hydroxide aggregates tagged with ^{99m}Tc (*3*). We have modified his procedure to reduce the amount of gelatin and to eliminate the need for pH determinations, thus resulting in a simpler, more rapid preparation.

MATERIALS AND METHODS

Reagents

1. Ferrous sulfate solution: 600 mg of $FeSO_4 \cdot 7H_2O$ is dissolved in 0.1 *N* HCl (prepared with sterile, pyrogen-free water) to a volume of 30 cc and sterilized by autoclaving. The solution is stable for 3 months.

2. Sodium hydroxide solution: 0.1 *N* NaOH is prepared by dissolving 400 mg NaOH in 100 ml of sterile, pyrogen-free water.

3. Gelatin 5%: 5 gm of gelatin (USP, type B) are dissolved in sterile, pyrogen-free water to a volume of 100 cc. The pH of the mixture after preparation and autoclaving is about 6.2.

4. 30-ml sterile, rubber-capped collecting vials.

Preparation of ^{99m}Tc-iron hydroxide aggregates

1. 0.5 ml of ferrous sulfate solution is transferred to a 30-ml vial. This solution contains 2 mg of iron.

2. 3.0 ml of sterile, pyrogen-free eluate containing ^{99m}Tc-pertechnetate is injected into the vial and mixed well.

3. $Fe(OH)_2$ is precipitated by adding 0.6 ml of 0.1 *N* NaOH. The final pH of this mixture is between 7.5 and 10.7.

4. After gentle mixing for 2 min, 1 ml of 5% gelatin is added to stabilize the particles. The final pH of the mixture to be injected into the patient is between 7.1 and 8.3.

5. The amount of free pertechnetate is determined by withdrawing 0.5 ml of the preparation. The activity in the solution is determined using an ionization-chamber dose calibrator. The solution is then centrifuged, an aliquot of the supernatant is measured and the percentage of free pertechnetate determined.

In 10 consecutive preparations, the mean pH of the mixture after the addition of NaOH was 8.3 ($\pm$0.9), the mean pH of the final mixture after the addition of gelatin was 7.3 ($\pm$0.4), and the mean percentage of free pertechnetate was 4% ($\pm$1%). The preparation time for the entire procedure is about 10 min.

RESULTS

Particle size. Particle size distribution was determined using a Coulter counter (Model B) which was calibrated for particle volume using ragweed pollen. The distribution of the particles with respect to diameter (assuming spherical particles) is shown in Fig. 1. The maximum number of particles occurs at 11–13 microns, and there are few particles greater than 30 microns. The concentration of particles with diameters > 4 microns in four consecutive preparations was 450,000 ($\pm$30,000) particles/cc of solution. Two cubic centimeters of solution (the maximum volume administered to a patient) contain 900,000 particles > 4 microns. There are about 280 billion capillary segments in the lung (*4*), and thus no more than 0.3×10^{-3}% of the capillaries can be occluded.

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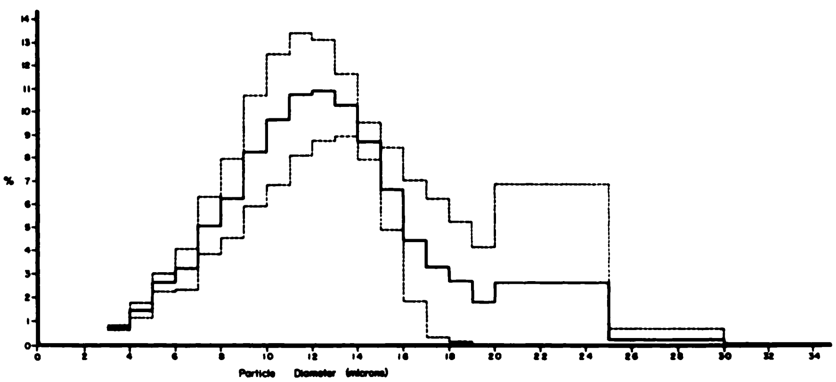

FIG. 1. Particle-size distribution of ^{99m}Tc-tagged iron hydroxide; mean of four preparations. Dashed lines represent ± 1 s.d. from mean distribution.

Organ distribution and clearance. Eight preparations of ^{99m}Tc-labeled iron particles were injected into New Zealand white male rabbits, and the distribution and clearance of radioactivity was studied at various time intervals. The rabbits, which had an average weight of 2.4 kg, were injected through an ear vein with about 0.5 cc of tagged particles (0.45–1.0 mCi) and sacrificed at 0.2, 4.8, 14 and 24 hr after injection. The lung, liver, spleen, kidney and thyroid were removed and weighed, and several weighed samples of each organ were counted with a Packard Auto-Gamma Spectrometer. Absolute activity was determined by comparison with standards prepared from the same batch of injected ^{99m}Tc-labeled particles. The results obtained from the rabbit studies are summarized in Table 1; they show an average lung uptake of 84% of the injected activity with less than 10% deposited in the liver and spleen. The lung-to-liver ratio of 11-to-1 indicates that the liver activity is low enough not to interfere with delineation of the inferior borders of the lung, and this has been verified in all clinical scans (Fig. 2).

The clearance of ^{99m}Tc from the lung can be represented by the sum of two exponential components, whose best-fit straight lines (on a semilog plot) were determined. The initial phase, representing about 27% of the injected dose, has a biological half-time clearance of 1.0 hr. The second phase, which is followed by about 60% of the injected dose, has a biological half-time clearance of 15 hr. Stern *et al* (*1*) have reported a half-time lung clearance of 10 hr for ^{113m}In-tagged iron hydroxide aggregates and 85% initial lung uptake.

The uptake of activity by the liver and spleen was highest at about 5 hr post-injection and then decreased slowly, with a half-time clearance from the liver of 32 hr. This is very similar to the reported behavior of ^{113m}In-iron hydroxide particles (*1*).

Stern *et al* (*1*) have measured the half-life of iron hydroxide particles labeled with ^{114m}In and ^{59}Fe and observed a longer half-life of approximately 18 hr for ^{59}Fe in the lung. Their results also suggested different fates for ^{114m}In and ^{59}Fe, the ^{114m}In being deposited mainly in the liver and spleen and the ^{59}Fe eventually clearing these organs and reaching a steady state in the blood after about 3 days. It is almost certain that the fates of ^{99m}Tc and the nonradioactive iron in our preparation are also dissimilar since the concentration of activity in the rabbit kidneys increased continually with time up to 24 hr (Table 1). A scintillation photograph of

TABLE 1. INTERNAL DISTRIBUTION OF ^{99m}Tc IN RABBITS AFTER INTRAVENOUS INJECTION OF ^{99m}Tc-LABELED IRON HYDROXIDE AGGREGATES

	% injected dose/organ at:				% injected dose/gm of organ at:			
Tissue	0.2 hr	4.8 hr	14 hr	24 hr	0.2 hr	4.8 hr	14 hr	24 hr
Lung	84(13)	47(5)	33(4)	19(8)	9.1(2.4)	5.4(0.9)	3.6(1.0)	2.1(0.5)
Liver	7.5(4.9)	30(7)	27(5)	20(1)	0.091(0.065)	0.38(0.10)	0.35(0.05)	0.26(0.03)
Spleen	0.26(0.22)	1.4(0.3)	0.62(0.10)	1.0(0.3)	0.16(0.16)	0.93(0.18)	0.80(0.06)	0.75(0.25)
Kidney	0.92(0.39)	1.5(0.1)	2.8(0.3)	4.7(0.2)	0.055(0.021)	0.11(0.01)	0.21(0.01)	0.28(0.02)
Thyroid	0.015(0.012)	0.084(0.077)	0.011(0.007)	0.030(0.018)	0.055(0.042)	0.26(0.23)	0.043(0.021)	0.14(0.10)
Blood					0.042(0.018)	0.015(0.009)	0.010(0.005)	0.005(0.001)
Carcass	7.1(3.7)	15(0.1)	10(1)	20(5)				

Each value is the mean of 3 rabbits, except for the shortest time interval when 7 rabbits were sacrificed.
The standard deviation is given in parentheses after each mean value.
Blood values represent the percentage of injected activity per cc of blood.

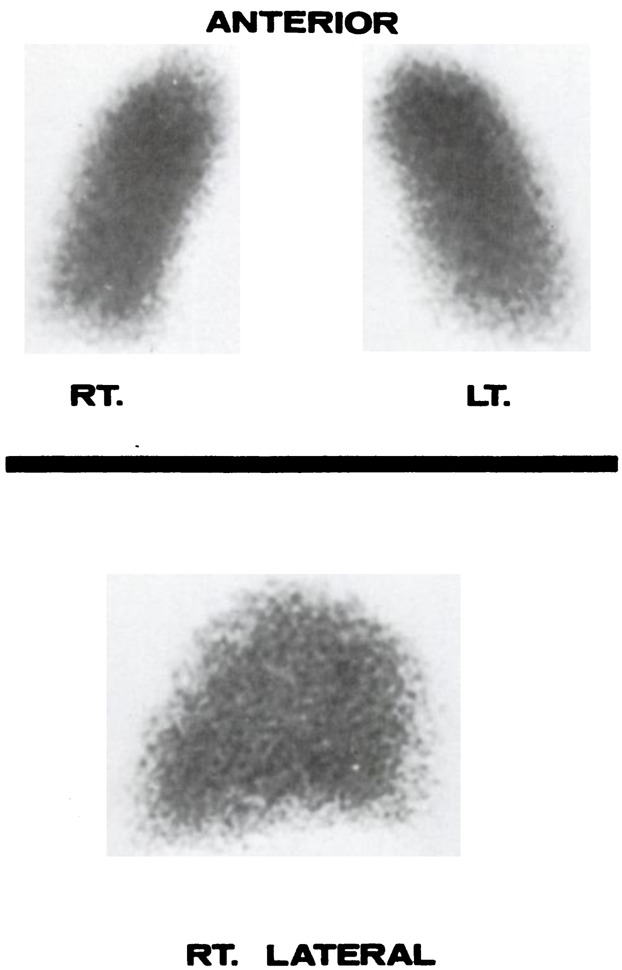

FIG. 2. Lung scintillation photographs taken with Pho/Gamma III using diverging collimator. For anterior and right lateral views, 400K and 300K counts were collected in 5½ and 8 min, respectively.

a rabbit taken 14 hr after injection showed that the residual activity is concentrated predominantly in lung and bladder, and on dissection the bladder was found to contain about 20% of the initial injected dose.

Toxicity. Studies on iron toxicity in mice and rabbits have been reported by Stern *et al* (*1*) and showed no adverse effects from doses up to 67 mg/kg of body weight. Since the maximum amount of iron in our preparation administered to a patient cannot exceed 20 μg/kg (for a standard 70-kg man), there is a safety factor with respect to iron of more than 3×10^3. Large quantities of gelatin (25–30 gm intravenously) have been used as plasma expanders (*5*). The maximum amount of gelatin in our preparation administered to a patient does not exceed 60 mg.

Radiation dose. The radiation dose delivered to the lung for complete elimination of ^{99m}Tc is estimated from Eqs. 1 and 2 for the beta and gamma components of the emitted radiations.

$$D_\beta(\infty) = 3.075\, E_\beta \Sigma C_0 T_{eff} \quad (1)$$
$$D_\gamma(\infty) = 3.075\, \Sigma n_i E_i \phi_i \Sigma C_0 T_{eff}. \quad (2)$$

E_β (MeV) is the total average beta-type energy released per disintegration and is 0.017 MeV for ^{99m}Tc (*6*). C_0 (μCi/gm) and T_{eff} (hr) are the initial activity concentration and the effective half-life for the two lung-clearance components determined from the rabbit studies. The absorbed fractions ϕ_i for each of the ^{99m}Tc gamma and x-ray energies E_i were extrapolated from published values of ϕ_i (*7,8*), assuming each lung to be a 500-gm flat ellipsoid. For 1 mCi of injected lung-scanning material, $D_\beta(\infty)$ is 150 mrads and $D_\gamma(\infty)$ is 110 mrads. An additional 20% of D_γ must be included in the dose estimate to account for backscattered radiation to the centrally situated lungs (*7,8*). The estimate of the total absorbed radiation dose to the lung from ^{99m}Tc-iron particles is therefore 280 mrads/mCi. This compares to 6,300 mrads/mCi for ^{131}I-macroaggregated albumin and 550 mrads/mCi for ^{113m}In-iron hydroxide (*9*).

Clinical results. Iron hydroxide particles labeled with indium have been widely used for pulmonary scanning in the past few years. Of the more than 1,500 lung scans which have been reported in the literature (*10–13*) no toxic, pyrogenic or hemodynamic effects have been observed. The only adverse reaction which has been encountered has been a transient flushing of the face immediately following injection lasting 5–10 min in three patients (*12*).

The ^{99m}Tc-iron hydroxide aggregates have been used by us in more than 100 cases in patients with a variety of lung diseases with no adverse reactions. Scans obtained with a 2-mCi dose of the preparation have been of excellent quality as Fig. 2 shows.

SUMMARY

A simple method for incorporating ^{99m}Tc into iron hydroxide particles using sterile, pyrogen-free reagents has been described. The compound consists of particles with a size distribution of 3–30 microns. Internal distribution studies using rabbits show that about 84% of the intravenously injected radioactivity is trapped by the lung, the remainder being deposited mainly in liver (7%) and carcass (7%). Clinical studies have resulted in excellent lung scans. Hazards from radiation and iron toxicity are considered to be negligible.

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