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Technetium-99m-Sulfur Colloid for Lymphoscintigraphy: Effects of Preparation Parameters

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There has been a resurgence in the use of lymphoscintigraphy for the external detection of lymph nodes for metastatic melanoma and breast tumors. Technetium-99m-antimony trisulfide colloid was the radiopharmaceutical developed for this procedure and was found to have a narrow distribution of small particles, 0.003-0.03 μm , but it was never approved by the FDA. Technetium-99m-sulfur colloid also forms particles and this article reports on the effects different preparation parameters have on its particle size distribution and stability. **Methods:** Four groups of kits were evaluated, kits which utilized: (a) a reduced heating protocol with a new $^{99\text{m}}\text{Tc}$ -elution, (b) a reduced heating protocol with an old $^{99\text{m}}\text{Tc}$ -elution, (c) a prolonged heating protocol with a new $^{99\text{m}}\text{Tc}$ -elution and (d) a prolonged heating protocol with an old $^{99\text{m}}\text{Tc}$ -elution. The particle size distribution and the stability of the different $^{99\text{m}}\text{Tc}$ -sulfur colloid kit preparations were evaluated over 6 hr utilizing polycarbonate filters ranging from 0.03 to 10 μm . **Results:** In vitro studies demonstrated no significant change in the particle size distribution over a 6-hr period and all $^{99\text{m}}\text{Tc}$ -sulfur colloid preparations had a bimodal particle size distribution pattern. Importantly, heating the kit for shorter periods of times utilizing [$^{99\text{m}}\text{Tc}$]pertechnetate, which had a longer ingrowth of [$^{99\text{m}}\text{Tc}$]pertechnetate, produced a formulation which had the largest percentage of particles smaller than 0.03 μm . **Conclusion:** In our clinical setting, $^{99\text{m}}\text{Tc}$ -sulfur colloid prepared with the reduced heating protocol and utilizing [$^{99\text{m}}\text{Tc}$]pertechnetate, which has the highest ingrowth of [$^{99\text{m}}\text{Tc}$]pertechnetate has proved to be an excellent agent for lymphoscintigraphy studies. This preparation has demonstrated rapid movement of the particles from the primary site to the lymph nodes in over 97% (106/109) of the patients we have studied.

Key Words: technetium-99m-sulfur colloid; lymphoscintigraphy; particle size distribution

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Increasing data suggest that the absence of tumor in the first node (sentinel node) in a nodal bed receiving lymph drainage from the primary malignant melanoma site predicts the absence of tumor in the other nodes of that bed. Biopsy of a single sentinel node is less costly and produces less morbidity than a

total lymph node dissection (1-4). Lymphoscintigraphy is an important diagnostic tool for the external detection of the sentinel node. To identify this node, tracer materials are injected around the primary melanoma site, the material is subsequently absorbed into the lymphatic vessels, where it flows through the lymphatic system into the lymph node bed where it becomes trapped. Morton et al. (4) demonstrated the usefulness of this procedure by making multiple intradermal injections of a blue dye to localize the lymph nodes. A limitation to the blue dye technique is that the dye is not visible through intervening tissue and therefore is not optimal for external detection of the labeled sentinel node.

Bergqvist et al. (5) reported that the particle size of a radiopharmaceutical utilized for lymphoscintigraphy greatly affects its biokinetics and that a particle size of less than 0.1 μm is necessary for migration from the injection site and uptake into the lymph nodes. The radiopharmaceutical initially developed for lymphoscintigraphy was $^{99\text{m}}\text{Tc}$ -antimony trisulfide colloid; however, this drug was never approved by the FDA for routine use in the United States and is no longer available even as an investigational agent. Technetium-99m-antimony sulfide colloid had a relatively narrow particle size distribution range, 0.003-0.03 μm (6). A second agent which has been utilized overseas is $^{99\text{m}}\text{Tc}$ -Nanocoll, which is a $^{99\text{m}}\text{Tc}$ -based agent which typically contains 95% of the colloidal particles smaller than 0.08 μm in size (7). No agent is available in the United States for lymphoscintigraphy which has the optimal particle size range, but other agents have been utilized for this study, including $^{99\text{m}}\text{Tc}$ -human serum albumin ($^{99\text{m}}\text{Tc}$ -HSA) and $^{99\text{m}}\text{Tc}$ -sulfur colloid. Technetium-99m-HSA has been utilized to successfully image flow, but it is not particulate in nature and there is less retention within the lymph nodes (5) and delayed images may miss the sentinel node.

In 1969, Hauser et al. (8) utilized a gelatin-stabilized $^{99\text{m}}\text{Tc}$ -sulfur colloid preparation and to image lymph nodes in rabbits. In addition, a recent report has suggested filtering a standard sulfur colloid preparation through a 0.1- μm membrane filter (9). The unfiltered $^{99\text{m}}\text{Tc}$ -sulfur colloid was reported to have an average particle size of 305-340 nm and, after filtration, was shown to have an average particle size range of 10 nm with a small (<0.1%) secondary population averaging 89-173 nm (9).

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A filtered preparation was reported to be successfully used for lymphoscintigraphy in 19 patients with suspected lymphedema (10). An alternative to filtering the standard ^{99m}Tc -sulfur colloid preparation would be to alter its labeling procedure to provide an agent which contains particles small enough to visualize the lymphatic drainage and particles large enough for prolonged retention within the nodal bed. This article reports on the effects that changes in preparation parameters have on a ^{99m}Tc -sulfur colloid kit.

MATERIALS AND METHODS

Kit Preparation

CIS-US (Bedford, MA) sulfur colloid kits are the only commercially available source for the preparation of ^{99m}Tc -sulfur colloid in the United States and were used for these studies. Four groups of kits were evaluated by reconstituting the lyophilized sulfur colloid kit with sodium pertechnetate, acidifying the reaction solution, heating for 3 or 10 min, allowing the vial to cool for 2 or 5 min, then neutralizing the reaction mixture. To test the effect of generator ingrowth, we used sodium pertechnetate from generator elutions, which had less than a 24-hr ingrowth of [^{99m}Tc]-pertechnetate period (new elution) before reconstitution of the kit and elutions in which the generator had an ingrowth period of [^{99m}Tc]-pertechnetate of 72 hr since the previous elution (old elution). Following the addition of 154.4 ± 5.7 mCi of sodium pertechnetate in 3 ml of normal saline to the reaction vial, syringe A, containing 1.5 ml 0.148 N HCl, was added and the vial was swirled. Two heating protocols were subsequently used: a reduced heating protocol in which the vial was heated in a rolling water bath for 1.5 min, gently agitated in the water bath and then heated for an additional 1.5 min in the water bath. After heating, the vial was cooled at room temperature for 2 min and then syringe B, which contained 1.5 ml of sodium biphosphate and NaOH to neutralize the reaction mixture, was immediately added. With the prolonged heating protocol after the addition of the pertechnetate and syringe A, the vials were heated for 10 min in a rolling water bath, allowed to cool for 5 min followed by the addition of syringe B. The four groups of kits evaluated ($n = 4$ in each group) included: (a) reduced heating with a new elution, (b) reduced heating with an old elution, (c) prolonged heating with a new elution and (d) prolonged heating with an old elution.

Radiochemical purity of each preparation was determined utilizing standard instant thin-layer chromatographic techniques. A small aliquot of the modified preparation of sulfur colloid was filtered through a 5- μm filter and the filtered product was spotted on ITLC-SG paper (Gelman Sciences, Ann Arbor MI) utilizing normal saline as the mobile phase. The percentage of particles which were retained on the 5- μm filter was also determined.

Stability Studies and Particle Size Determination

To determine the particle size distribution and the stability of the ^{99m}Tc -sulfur colloid particles formed during preparation, kits were prepared as described above utilizing both heating techniques and "old" and "new" elutions. Nine vials were studied at 15, 30, 60, 120, 240 and 360 min postreconstitution. At each time point, a 0.05–0.1-ml sample of the ^{99m}Tc -sulfur colloid preparation was placed on 10-, 5-, 2-, 0.8-, 0.4-, 0.2-, 0.08-, 0.05- and 0.03- μm Nuclepore filters (Costar Inc, Cambridge MA). To filter the samples through the polycarbonate filters, 15 ml of normal saline was used for each filter. The percent of the total activity retained on each of the filters and in the filtrate was determined using a dose calibrator. The remaining vials ($n = 7$) were prepared as described above, but particle sizes were evaluated at 60 and 360 min postreconstitution.

Statistical Analysis

We used analysis of variance (ANOVA) with Tukey's method for multiple comparisons and Student's t-test for comparisons between two groups. Significant difference was defined as a p value of less than 0.05.

RESULTS

Prolonged heating of the kit produced a formulation that had a slightly, but significantly, higher ($p = 0.0006$) radiochemical purity: $99.68\% \pm 0.34\%$ for the 10-min preparation compared to $97.10\% \pm 1.14\%$ for the 3-min boiling time. The percentage of particles larger than 5 μm was determined by passing a sample of each kit through a filter needle. With the 3-min boiling time, the percentage of particles greater than 5 μm averaged 4.35%, which was not significantly different ($p = 0.79$) when compared to the 10-min boiling time, which averaged 4.52%.

The particle size stability studies demonstrated that there were no significant changes in particle size distribution over the 6-hr study period ($p > 0.05$). The results of the particle size distribution studies are listed in Table 1 and illustrated in Figure 1. Table 1 lists the particle size ranges and the percent of particles in each range for each of the preparation protocols. Reduced heat refers to a 3-min heating period followed by a 2-min cooling period. Prolonged heating refers to a 10-min boiling period followed by a 5-min cooling period. New technetium refers to preparation of the kit formulation with technetium that has less than a 24-hr ingrowth period, whereas old technetium refers to technetium that has a 72-hr ingrowth of [^{99m}Tc]-pertechnetate. Figure 1 is a graph of the percent of particles versus the particle size range for each of the four different preparation parameters and clearly demonstrate that all preparations of ^{99m}Tc -sulfur colloid have a bimodal distribution pattern regardless of the preparation procedure used.

DISCUSSION

Technetium-99m-sulfur colloid is a colloidal particle which, after intravenous injection, is routinely used for liver and spleen imaging. Its successful use in this area has required an understanding of the basic chemistry involved in the preparation of this radiopharmaceutical agent. Larson et al. (11) reported that upon heating there is rapid incorporation of ^{99m}Tc into the sulfur colloid particles. Therefore, it is possible to heat the reaction for shorter periods of time and still obtain excellent labeling efficiency. This finding is consistent with our studies in which excellent radiochemical purity was obtained with heating for 3 min and cooling for 2 min. Historically, there have been several methods of producing ^{99m}Tc -sulfur colloid particles by using various starting materials and stabilizing agents. The most common reagent uses sodium thiosulfate as a source of sulfur and various types and amounts of stabilizing agents. These ingredients have been used in different amounts to develop kits that produce the appropriate particle size and have different degrees of stability (12–14). Because there is only one commercially available kit of sulfur colloid in the United States, we thought it was important to understand particle size and stability of this ^{99m}Tc -sulfur colloid preparation. The particle size distribution of the CIS kit formulation did not change over a 6-hr period.

The nucleation process of the reaction has been studied (15) and it has been suggested that the technetium colloid forms more rapidly than a sulfur colloid (15). Thus, the sulfur colloid forms at least in part on the ^{99m}Tc -colloid which serves as its nucleus. In addition, some sulfur nuclei will also form independently. Therefore, the smaller particles generally contain relatively low amounts of sulfur but a significant amount of

TABLE 1
Percent of Particles in Various Size Ranges in Different Preparation Procedures

| Particle size range (μm) | Reduced heat new technetium (%) | Reduced heat old technetium (%) | Prolonged heat new technetium (%) | Prolonged heat old technetium (%) |
|---------------------------------------|---------------------------------|---------------------------------|-----------------------------------|-----------------------------------|
| >10 | 4.99 \pm 1.94 | 4.52 \pm 0.51 | 4.47 \pm 0.98 | 4.58 \pm 1.37 |
| 5-10 | -0.19 \pm 1.04 | 0.36 \pm 0.54 | 0.64 \pm 0.86 | 1.13 \pm 0.59 |
| 2-5 | 2.48 \pm 0.69 | 1.22 \pm 1.05 | 2.16 \pm 0.21 | 1.90 \pm 1.12 |
| 0.8-2* | 6.38 \pm 0.37 | 4.91 \pm 0.57 | 37.60 \pm 5.67 | 16.75 \pm 5.95 |
| 0.4-0.8† | 17.57 \pm 5.67 | 16.54 \pm 5.08 | 35.05 \pm 3.40 | 27.99 \pm 6.24 |
| 0.2-0.4‡ | 25.39 \pm 5.51 | 20.78 \pm 4.28 | 3.27 \pm 1.62 | 6.41 \pm 1.47 |
| 0.08-0.2‡ | 6.23 \pm 1.58 | 4.87 \pm 0.75 | 1.04 \pm 1.32 | 1.07 \pm 1.54 |
| 0.05-0.08 | 0.09 \pm 0.35 | 0.53 \pm 1.70 | 0.26 \pm 0.28 | 0.59 \pm 1.42 |
| 0.03-0.05 | 0.99 \pm 1.35 | -0.33 \pm 1.12 | 0.87 \pm 0.20 | 2.86 \pm 1.17 |
| <0.03§ | 36.18 \pm 4.90 | 46.65 \pm 7.69 | 14.66 \pm 6.70 | 36.74 \pm 3.36 |

*Significant differences between all four groups.

†Significantly smaller percent of particles between a reduced heating time with new or old generator elutions compared to prolonged heating with a new elution. Also, there is a significant difference between the percent of particles using a reduced heating time with an old elution compared to a prolonged heating time and an old elution.

‡Significant higher percent of particles between the reduced and the prolonged heating regardless of the age of the elution.

§Reduced heating procedure and an old elution produced significantly higher percentage of small particles. Prolonged heating with new technetium produced the smallest percentage of small particles.

All values are mean \pm 1 s.d.

technetium (15). In the present study, with pertechnetate that had longer ingrowth of $^{99\text{m}}\text{Tc}$ in the elution, the number of smaller particles increased potentially due to an increase in the number of $^{99\text{m}}\text{Tc}$ and $^{99\text{m}}\text{Tc}$ -colloid nuclei formed. In kits that had prolonged heating times, we observed that the percentage of larger particles did increase. However, in kits with prolonged heating and old elutions, the percentage of small particles was not significantly different than that observed when heating for a shorter period of time utilizing pertechnetate that had less $^{99\text{m}}\text{Tc}$ -present (new elution).

The importance of particle size for lymphoscintigraphy studies has been reported (5). The particles should be larger than 0.004–0.005 μm in size, because smaller particles have been reported to penetrate the capillary membranes and therefore may be unavailable to migrate through the lymphatic channel (16). Particles smaller than 0.1 μm demonstrate the most rapid flow from the injection site with significant retention in the lymph node for up to 5 hr. In addition, larger particles, approximately 500 μm , demonstrated a much slower rate of clearance from the injection site, with a significantly lower

accumulation in the lymph nodes. The use of a reduced heating protocol results in a dramatic increase in the percentage of particles smaller than 0.4 μm , 70.86%, regardless of the age of the generator elution. On the other hand, prolonged heating significantly decreases the percentage of small particles, 20.10% with new technetium and 47.67% with old pertechnetate. These studies demonstrate that there is bimodal distribution of labeled particles in a $^{99\text{m}}\text{Tc}$ -sulfur colloid kit and in order to provide an optimal imaging agent, the sulfur colloid kit should be prepared with a reduced heating protocol and [$^{99\text{m}}\text{Tc}$]pertechnetate that has higher levels of [$^{99\text{m}}\text{Tc}$]pertechnetate. In addition, this preparation does not appear to form a significant amount of particles smaller than 0.004 μm , in that there was no visualization or localization of activity outside of the lymphatic system in all of the studies.

CONCLUSION

These studies demonstrate that length of heating and cooling and the time since the last generator elution are factors that affect the particle size of $^{99\text{m}}\text{Tc}$ -sulfur colloid and thus may

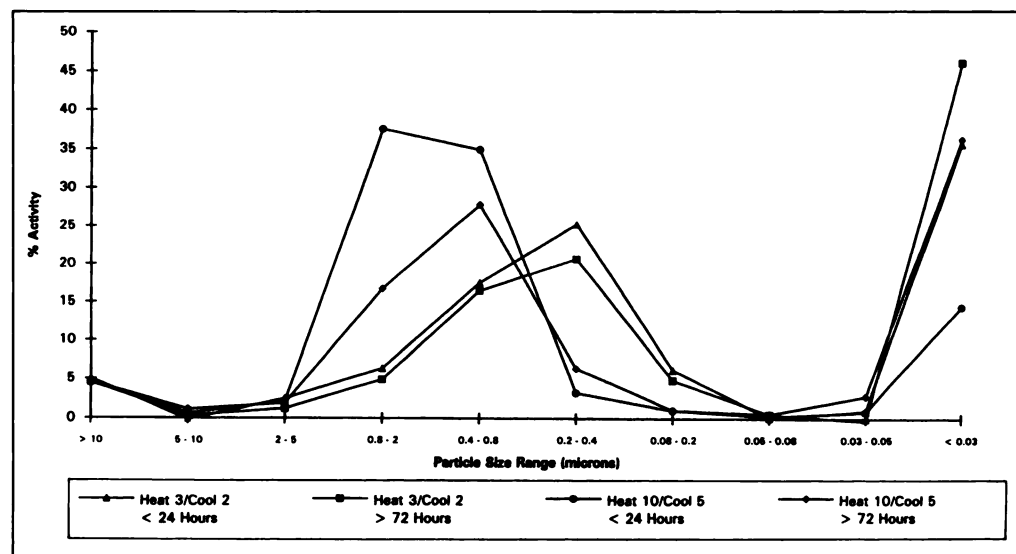


FIGURE 1. Particle size distribution of $^{99\text{m}}\text{Tc}$ -sulfur colloid using new and old generator elutions and two different preparation methods. Vials were prepared by heating for 3 min and cooling for 2 min or heating for 10 min and cooling for 5 min with a new or old generator elution. A new generator elution refers to an ingrowth of $^{99\text{m}}\text{Tc}$ less than 24 hr. Old elution refers to ingrowth of $^{99\text{m}}\text{Tc}$ which is 72 hr old.

affect the rate of migration from the injection site. To maximize the rate of migration and the overall migration success rate of the tracer to the sentinel node in our clinical setting, we used kit preparations in which the ^{99m}Tc -sulfur colloid was heated for 3 min, allowed to cool for 2 min and used pertechnetate that had the highest amount of ingrowth of [^{99m}Tc]pertechnetate. Use of this preparation procedure in addition to withdrawing the patient dose through a sterile 5- μm filter and making 4–6 intradermal injections, 50–100 μl each, around the primary site, resulted in an excellent agent for lymphoscintigraphy studies for malignant melanoma. We have successfully imaged 97% (106/109) of our patients and have also used rapid dynamic scans to map and image the lymphatic drainage system (17–20). In addition to rapid movement, the preparation demonstrated prolonged retention within the nodes. At our institution, this preparation, in combination with imaging and a gamma handheld detector, plays an important role in the detection, localization and excision of the sentinel node.

Currently, several studies are underway to identify additional methods that would further reduce the average particle size formed during the preparation of ^{99m}Tc -sulfur colloid. Particle size studies utilizing [^{99m}Tc]-sodium pertechnetate obtained from generators having up to 7 days of ingrowth of [^{99m}Tc]-pertechnetate are currently being investigated. Also, studies in which an additive is placed into the kit before heating, which provides more nucleation sites for particles to form, are underway.

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Technetium-99m-Tetrofosmin as a Substrate for P-Glycoprotein: In Vitro Studies in Multidrug-Resistant Breast Tumor Cells

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The accumulation of ^{99m}Tc -tetrofosmin (TFos) was studied in wild-type (WT) and doxorubicin-resistant (Adr^{R}) variants of the rat MatB and human MCF-7 breast tumor cell lines to determine whether TFos, like ^{99m}Tc -sestamibi (MIBI), is a substrate for P-glycoprotein (P-gp), a multidrug-resistance transporter. **Methods:** The time course of accumulation of TFos and MIBI in WT and Adr^{R} cells over 1 hr was studied using single-cell suspensions at 1×10^6 cells/ml incubated at 37°C in the presence or absence of PSC833, a potent modulator of P-gp. Modulator dose-response curves were generated for PSC833, cyclosporin A, and verapamil. **Results:** In both MatB and MCF-7 cells, TFos and MIBI accumulated extensively in

WT cells and accumulation was not affected by PSC833. In contrast, Adr^{R} cell lines accumulated very little of either tracer, but addition of PSC833 or other modulator increased this accumulation in a dose-dependent fashion. TFos and MIBI did not differ significantly in their behavior. **Conclusion:** TFos shares with MIBI the property of being a substrate for P-gp and thus TFos may be useful for functional imaging of tumor P-gp status.

Key Words: technetium-99m-tetrofosmin; technetium-99m-sestamibi; multidrug resistance

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Multidrug resistance (MDR) involving overexpression of P-glycoprotein (P-gp), a transmembrane pump which acts as a natural defense mechanism by pumping xenobiotics out of

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