Clinical Comparison of Two Radiocolloids for Internal Mammary Lymphoscintigraphy

W. D. Kaplan, C. W. Piez, R. S. Gelman, S. M. Laffin, E. M. Rosenbaum, C. A. Jennings, C. A. McCormick, J. R. Harris, I. C. Henderson, and H. L. Atkins

Divisions of Nuclear Medicine, Biostatistics, and Epidemiology, and Departments of Radiation Therapy and Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

Recent studies suggest that ^{99m}Tc-labeled radiocolloid (SC) compounded with hydrogen sulfide can be used to visualize lymph channels and nodes. Our study prospectively compared SC with ^{99m}Tc antimony sulfide (SbS) colloid, in 28 patients undergoing internal mammary lymphoscintigraphy. Images were recorded on a scintillation camera and computer at 0.5, 1.0, and 3.0 hr. Quantitative analysis included assessment of percent (%) injected dose in nodes, the percent remaining at the injection site, and the relative intensity of the most cephalad node compared to a ^{57}Co standard. The mean ($\bar{x}$) % injected dose of both radiocolloids within visualized nodes was less than 1% at each time interval, with no significant differences between $\bar{x}$'s. The $\bar{x}$ % injected dose remaining at the injection site at 3.0 hr was 83 for SbS and 76 for SC not statistically significant (N.S.). The $\bar{x}$ of the ratio of counts within the most cephalad node at 3.0 hr to counts within a ^{57}Co standard was 0.98 for SbS and 1.03 for SC (N.S.). Clinical assessment of number of nodes visualized and extent of radiocolloid migration showed no difference between the two agents. The biological and clinical parameters for the two colloids appear similar when used for internal mammary lymphoscintigraphy.

J Nucl Med 26:1382–1385, 1985

Radionuclide lymphoscintigraphy offers a noninvasive and physiologic method for delineating regional lymph node drainage. The technique is performed following interstitial administration of inert colloids, the behavior of which appears strongly related to particle size (*1*).

Of the many technetium-99m-(^{99m}Tc) labeled agents utilized, antimony sulfide colloid (SbS)*, that which is most widely employed, shows the greatest percent uptake in lymph nodes (*2*). However, Dunson et al. (*3*) indicated that a ^{99m}Tc-labeled radiocolloid (SC)† compounded with hydrogen sulfide and exhibiting a particle size of < 100 nm could be used to visualize pelvic and abdominal lymph node groups following injections into the medial web space of the feet. Since this initial description, ^{99m}Tc-labeled SC has been used extensively for intradermal injections to define lymphatic drainage in patients with malignant melanoma (*4*).

To date, however, no quantitative or qualitative data exist comparing SC to SbS for radionuclide lymphoscintigraphy of the internal mammary lymph nodes. This study prospectively evaluated 28 patients with breast cancer who presented to our institution for internal mammary lymphoscintigraphy as part of the planning procedure associated with radiation therapy.

Received July 19, 1985; revision accepted Aug. 28, 1985.

For reprints contact: William D. Kaplan, MD, Div. of Nuclear Medicine, Dana-Farber Cancer Institute, 44 Binney St., Boston, MA 02115.

MATERIALS AND METHODS

Patients

Thirty-one consecutive female patients were entered on the study. Three did not have an adequate initial injection (see below) and were not included in the analysis. The remaining 28 patients ranged in age from 32–76 yr (median 52 yr). Twenty-five of the 28 were 2–12 wk post-"lumpectomy," two were 6 wk and 6 yr postmastectomy, and one was immediately postbiopsy. Fourteen patients were axillary node positive for tumor (seven in each radiocolloid group), nine were axillary node negative, and five had unknown axillary node status at the time of imaging.

Radiocolloids

Technetium-99m Sb_2S_3. The contents of the radiocolloid preparation included 0.2 ml of sterile 0.5N hydrochloric acid; 0.67 mg Sb_2S_3; 3.2 mg povidone; 1.0 mg potassium tartate; 1.2 ml sterile water; 24.7 mg dibasic sodium phosphate; 2.7 mg monobasic sodium phosphate; 0.5 ml sterile water.

This radiocolloid was aseptically prepared with 0.5 ml of sodium pertechnetate (^{99m}Tc) in isotonic saline up to 15 mCi, according to the manufacturer's instructions.

Technetium-99m SC. The contents of the radiocolloid preparation included: suspension of 4.0 mCi of ^{99m}Tc SC/ml; 2 mg of gelatin stabilizer/ml; HCl and NaOH to adjust the final pH to a range of 4-7.

The radiocolloid was aseptically prepared by reacting with sodium pertechnetate (^{99m}Tc) in acid solution from which the excess was expelled. By this method of preparation, an insoluble sulfide colloid formed which was essentially "no-carrier-added." This sulfur colloid preparation was therefore different from others which contain sufficient excess material to form larger particles.

This radiocolloid was delivered from a commercial supplier in a form ready for injection.

Radiocolloid administration

Injection technique. The anatomic site and technique for radiocolloid injection have been previously described (*5*). Between 0.5–1.0 mCi of [^{99m}Tc]radiocolloid, in a volume of ~0.2 ml, was injected. With the patient in a supine position, the injection was administered at a point ~3 cm inferior to the xyphoid process and 1–2 cm medial to the midclavicular line on the side to be evaluated. A tuberculin syringe (1.0 ml) fitted with a 22-gauge, 1 1/2-in. needle was held at an angle 45° from the horizontal with the needle directed toward the axilla on the side to be examined. The depth of the injection was controlled by applying tension to the skin and underlying rectus muscle with the opposite hand. Radiocolloid was deposited ~2 cm deep to the skin, just anterior to the posterior rectus sheath.

Injectate assessment

Immediately after administration of radiocolloid, the injection site was imaged to ensure that the injectate had been deposited at the correct location.

To verify the depth of radiocolloid injection, the supine patient was imaged in a cross-table lateral projection with the skin surface defined by a radioactive marker. In this projection, an optimal injection showed a noticeable separation between the skin marker and injectate. Any patient who did not display this configuration and therefore required a second injection for clinical purposes was eliminated from the study (three patients).

Imaging

Technique. Ten-minute images were obtained at time 0, at 0.5, 1.0, and 3.0 hr following injection; a 10-in. field-of-view, 37 photomultiplier tube, low-energy mobile camera fitted with a diverging collimator was used.‡ The diverging collimator allowed incorporation of the injection site, full length of the internal mammary lymph node chain and sternal notch cobalt-57 (^{57}Co) marker in a single field-of-view.

Images were simultaneously recorded on a PDP-11/34§ computer in a 64 × 64 word mode for later quantitative analysis.

Data analysis

Qualitative assessment. The number of internal mammary nodes seen per patient and the level of radiocolloid migration for each patient were recorded.

Quantitative assessment. The percent uptake in all internal mammary nodes per patient was calculated for each of the three time intervals as was the percent injected dose remaining at the injection site at 3 hr. All data were corrected for physical decay. No corrections were made for tissue attenuation since the two patient groups were matched for weight and nodal depth (*6*) (Table 1).

No nodes were at a depth greater than 5.0 cm therefore there was at most a 15% reduction in sensitivity due to the use of a diverging compared with a parallel-hole collimator. Since the two patient groups were equally matched with regard to weight and nodal depth, use of a diverging collimator did not result in any disparity in quantitative information.

To quantitate the relative intensity of the most cephalad node and allow a comparison of this intensity between the two radiocolloids under evaluation, the ratio of counts within the most cephalad node to the decay-corrected counts obtained from the ^{57}Co marker was calculated at the 3-hr time period.

Statistical methods. Confidence intervals on differences between means were calculated using the normality assumption. The two-sided, two-sample Wilcoxon test (*7*)

TABLE 1
Physical Characteristics of Patients Undergoing Radionuclide Lymposcintigraphy

Item	SbS	SC
Weight		
Mean	156 ± 27	147 ± 30
Median	147	152
Range	110 - 215	110 - 217
Nodal depth (cm)		
Mean	2.28 ± 0.84	2.75 ± 1.20

TABLE 2
Scintigraphic Data in 28 Patients Undergoing Internal Mammary Lymphoscintigraphy with [^{99m}Tc] SbS and SC

Radiocolloid	Scan interpretation: Normal	Scan interpretation: Abnormal	No. nodes seen ($\bar{x}$/pt)*	Migration to S.N.† (% pts)
[^{99m}Tc]SbS	11	3	6.5	64
[^{99m}Tc]SC	13	1	7.1	79

*Mean/patient.
†S.N. = Sternal notch.

was used to compare the two agents with respect to number of nodes visualized, percent injected dose within lymph nodes, percent injected dose remaining at injection site at 3 hr, and ratio of counts within the most cephalad lymph node and the ^{57}Co standard. The comparison of patients with respect to the level of radiocolloid migration used the two-sided Fisher exact test (*8*).

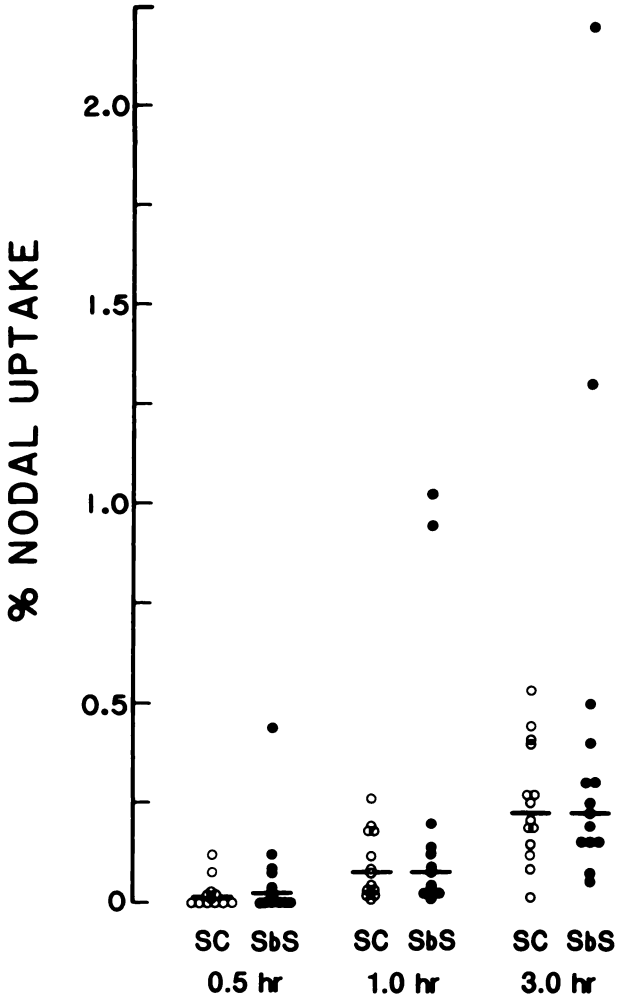

FIGURE 1
Percent of injected dose of SC and SbS within lymph nodes

TABLE 3
Injected Dose (%) at Injection Site at 3 hr

Radiocolloid	No. pts.	Mean	Range	Median
[^{99m}Tc]SbS	14	83	74–100	87
[^{99m}Tc]SC	14	76	49–95	76

RESULTS

Qualitative assessment

Qualitative assessment of the internal mammary chain demonstrated progressive migration of both radiocolloids from proximal to distal nodes as a function of time.

The mean number of lymph nodes visualized at 3 hr (xyphoid to sternal notch) was 6.5 for SbS patients (11 normal and three abnormal scans¶)and 7.1 for the SC patients (13 normal and one abnormal scan¶). This difference was not significant (p=0.82). Sixty-four percent of patients administered SbS showed migration to the level of the sternal notch, while 79% injected with SC showed migration to this level. This difference was not significant (p=0.68) (Table 2).

Quantitative assessment

The mean percent of injected dose of SbS within lymph nodes (visualized nodes from the xyphoid to the sternal notch) was 0.06, 0.21, and 0.45 at 0.5, 1.0, and 3.0 hr; the mean percent of injected dose of SC within lymph nodes was 0.02, 0.09, and 0.25 at these times (Fig. 1). For the two colloids, the percent uptake decreased progressively within nodes as a function of distance from the injection site. The differences were not significant at any of the three sampling times (p=0.09, 0.66, 0.78). Ninety-five percent confidence intervals on the difference of the means (SbS - SC) were -0.03 to 0.11, -0.08 to 0.32, and -0.23 to 0.43 at 0.5, 1.0, and 3.0 hr.

The mean percent injected dose remaining at the injection site at 3 hr was 83% for SbS and 76% for SC. This difference was not significant (p=0.13). The 95% confidence interval for the difference in means was -2.14 to 17.6 (Table 3).

The medians of the ratios of counts within the most cephalad lymph node at 3 hr to the counts in the ^{57}Co standard were 0.68 for SbS and 0.38 for SC. The means were 0.98 and 1.03, respectively; this difference was not significant (p=0.87). The difference between median and mean values was due to one or two unusually high ratios in each group (Table 4).

TABLE 4
Ratio of Cephalad Nodal Counts to ^{57}Co Standard at 3 hr

Radiocolloid	No. pts.	Mean	s.d.*	Median	Range
[^{99m}Tc]SbS	14	0.98	1.60	0.68	0.17–6.34
[^{99m}Tc]SC	13	1.03	1.64	0.38	0.10–5.84

*s.d. = Standard deviation.

DISCUSSION

In a number of centers, radionuclide lymphoscintigraphy has become an integral part of the clinical practice of nuclear medicine. The tracer approach to lymphatic visualization offers the clinician an opportunity to image inaccessible groups of lymph channels and nodes, and to clinically assess the functional status of a hitherto obscure drainage system. With the growing interest in this technique, investigators have used a variety of radiopharmaceuticals in an effort to achieve optimal lymph channel and lymph node visualization (*9–13*).

Although the labeled colloid particles used for clinical imaging of the reticuloendothelial system can approach 600 nm in diam, those most commonly utilized for interstitial lymphoscintigraphy are < 100 nm in diam (*1*). Differences in biokinetic behavior and percent uptake within lymph nodes exist depending upon which radiocolloid is utilized and this disparity seems related to the diameter of the particles.

In the search for a radiopharmaceutical which shows both greater nodal uptake and greater clearance from the injection site than does [^{99m}Tc]SbS, [^{99m}Tc]SC has been suggested as a potentially useful colloid. Results of our study show that although SbS allowed an approximate twofold increase in the mean percent injected dose within internal mammary nodes at 3 hr, the medians were almost identical and the difference was not statistically or clinically significant. Neither the percent of injected dose remaining at the injection site, the total number of nodes visualized, nor the level of migration was statistically different for the two groups of patients. Our data suggest that the biological and clinical parameters for the two radiocolloids are similar; additional patient studies will be needed to confirm these initial observations.

FOOTNOTES

*Cadema Medical Inc., Middletown, NY.
†Medi-Physics, Inc., Richmond, CA.
‡Siemens Medical Systems Inc., Iselin, NJ.
§Digital Equipment Corp., Waltham, MA.
¶Normal scans demonstrated uniform uptake throughout lymph node chain whereas abnormal scans showed decreased nodal uptake, attenuated and collateralized channels (*5*).

ACKNOWLEDGMENTS

The authors thank Diane Brennan for her assistance in the preparation of this manuscript.

REFERENCES

1. Bergqvist L, Strand ES, Persson BRR: Particle sizing and biokinetics of interstitial lymphoscintigraphic agents. *Semin Nucl Med* 13:9–19, 1983
2. Strand ES, Persson BRR: Quantitative lymphoscintigraphy I: Basic concepts for optimal uptake of radiocolloids in the parasternal lymph nodes of rabbits. *J Nucl Med* 20:1038–1046, 1979
3. Dunson GL, Thrall JH, Stevenson JS, et al: ^{99m}Tc minicolloid for radionuclide lymphoscintigraphy. *Radiology* 109:387–392, 1973
4. Bennett LR, Lago G: Cutaneous lymphoscintigraphy in malignant melanoma. *Semin Nucl Med* 13:61–69, 1983
5. Ege GN: Internal mammary lymphoscintigraphy: The rationale, technique, interpretation and clinical application: A review based on 848 cases. *Radiology* 118:101–107, 1976
6. Siddon RL, Chin, LM, Zimmerman RE, et al: Utilization of parasternal lymphoscintigraphy in radiation therapy of breast carcinoma. *J Rad Oncol Biol Phys* 8:1059–1063, 1982
7. Hollander M, Wolfe DA: *Nonparametric Statistical Methods*, New York, John Wiley & Sons, 1973, pp 68–74
8. Cox DR: *Analysis of Binary Data*, London, Methuen Co., 1970, pp 48–52
9. Kaplan WD, Davis MA, Rose CM: A comparison of two technetium-99m-labeled radiopharmaceuticals for lymphoscintigraphy: Concise communication. *J Nucl Med* 20:933–937, 1979
10. Ege GN, Warbick A: Lymphoscintigraphy: A comparison of antimony sulfide colloid and ^{99m}Tc stannous phytate. *Br J Radiol* 52:124–129, 1979
11. Hultborn KA, Larson LG, Raghult I: The lymph disease from the breast to the axillary and parasternal lymph nodes studied with the aid of colloid Au-198. *Acta Radiol* 43:52–64, 1955
12. Bruun P: Standardized sterile kits for preparation of labeled albumin, macroalbumin, iron ascorbic acid complex, and antimony sulfide colloid. *Scand J Clin Lab Invest* 28:313–319, 1971
13. Gallagher BM, Delano ML, Watt R, et al: A comparison of radiopharmaceuticals for lymphoscintigraphy. *J Nucl Med* 21:P36, 1980 (abstr)