An Improved Method of Sulfur Colloid Radioaerosol Nebulization

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Radioaerosols have been used experimentally for a number of years as lung imaging agents. However, adherence of particles of rhenium-stabilized Tc-99m sulfur colloid within air-blast nebulizers has limited their usefulness. We have devised a method to reduce the surface charge on the particles, and thus their adherence, by addition of human serum albumin. This intervention does not alter the aerodynamic characteristics of the aerosol.

Technetium-99m sulfur colloid is commonly used to image the liver and spleen (*1*) and can be used in aerosol form in lung studies (*2–4*). The aerosol is most often generated from liquid colloid suspensions by air-blast or ultrasonic nebulizers. However, in air-blast systems, the aerosols produced are highly charged (*5*), so that a varying but usually high proportion of the colloid adheres within the nebulizer. This significantly reduces the amount of activity deposited in the target organ, necessitating use of a large dose (20–60 mCi) to transfer a sufficient quantity into the lungs for imaging with a scintillation camera (*3,4*). Siliconizing the nebulizer does not retard adherence.

Several formulations of sulfur colloid have been used in attempts to overcome this problem. The colloid particle is produced by heating sodium pertechnetate and sodium thiosulfate in acid medium, then adding a buffer to neutralize the solution and prevent the formation and growth of additional particles. Sulfur colloid particles thus produced tend to form aggregates, which adhere to glass surfaces in a manner comparable to the precipitation of gold sol. (A sol is a colloidal suspension of particles.)

The gold sol particle has a net negative charge on the surface. Addition of NaCl to an aqueous solution neutralizes the particles, which then aggregate to form a precipitate. If a protective substance such as gelatin is added to prevent precipitation, the protein is attracted to the particle and the subsequent addition of NaCl can only partly reduce the charge on the sol; i.e., the system is less readily precipitated.

The aggregation of sulfur colloid particles can be prevented by adding rhenium or gelatin (*7*), dextran (*8*), or human serum albumin (HSA) (*9*). The protective substance, which is incorporated into the particles during their formation and imparts a net negative charge to their surface, reduces adherence to glass surfaces.

With few exceptions (*2*), reports of aerosol studies have not specified how the colloid was prepared. We use rhenium as the carrier substance; the resulting formulation is a stable and radiochemically pure product. Despite this stabilization, the loss of aerosol by adherence to the inner surface of the nebulizer was large, on occasions exceeding 90% of initial activity (Fig. 1). We therefore experimented with the addition of HSA to the nebulizer mixture.

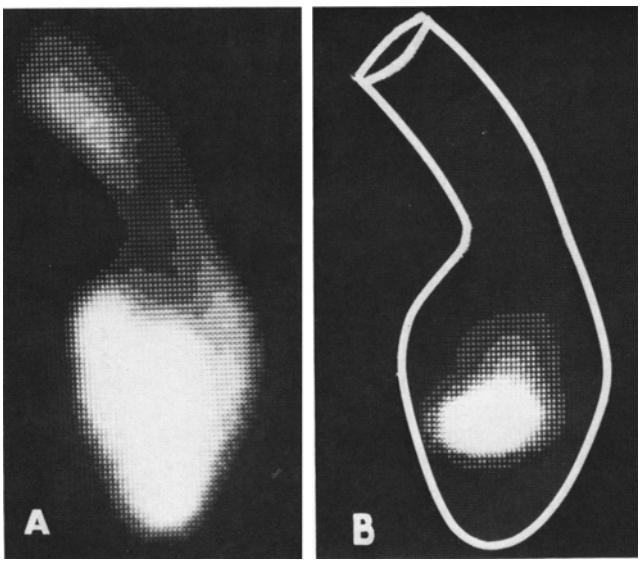

FIG. 1. (A). Technetium sulfur colloid adhering to nebulizer in standard solution. (B). Modified preparation of colloid to which HSA has been added. Both nebulizers had identical initial volumes and specific activities, and were operated for same time period. Remaining bulk solution was removed before these images were taken by a gamma camera.

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Method

Our method of preparing sulfur colloid throughout the experiments was as follows:

To a solution containing 18 mg of sodium thiosulfate pentahydrate and 3.75 mg of sodium perrhenate in 3-ml volume is added 9 ml of sodium pertechnetate solution and 1.5 ml of 1N HCl. The solution is heated in a boiling water bath for 3 min, 15 sec. Then 4.5 ml of phosphate buffer is added to neutralize the pH of the final preparation to approximately 7. Binding of the preparation is between 95 to 98% complete as analyzed by thin layer chromatography (Gelman ITLC-SG) in a normal saline solvent.

Our study was performed on healthy volunteers and on patients with chronic obstructive pulmonary disease. Signed informed consents were obtained from both groups.

An air-blast nebulizer (De Vilbiss, Somerset, PA) was operated at 30 psi to generate aerosols of rhenium-stabilized Tc-99m sulfur colloid. In 11 of the 25 experiments, we added 0.05 ml of 25% HSA to 2 ml of the sulfur colloid solution (specific activity: 5–6 mCi/ml [185–220 MBq/ml] immediately before use). The aerosol was channeled through a reservoir bag and inhaled by each subject.

The average amount of radioactivity deposited in the lungs of all subjects was estimated to be 0.8 mCi (30 MBq). These estimates were based on the count rate observed from the injection of a known amount of Tc-99m labeled macroaggregated albumin in three subjects.

Results

Both with and without HSA, the activity median aerodynamic diameter of the sulfur colloid aerosol (sized with a Cascade impactor, Andersen Sampler, Inc., Atlanta, GA) was 1.2 μm and the associated geometric standard deviation was 1.8.

TABLE 1. Measurement of Inhalation Volume and Activity Deposited in Lungs of Subjects Receiving Sulfur Colloid Aerosol with no Albumin Added

Subject	Total volume inhaled (l)	Initial activity in nebulizer (MBq)	Activity deposited in lungs (MBq)
WL1	24.4	851	56
PM	30.5	932	33
DR	29.4	1099	44
KH1	27.7	1061	48
MY	24.4	1117	56
HY	30.7	1099	44
RH*	30.1	784	22
RS*	32.0	673	26
JH*	35.7	888	15
LW*	28.8	825	11
WL2	34.6 (est.)	1099	15
DH	49.4	1362	22
KH2	39.2	981	21
KM	98.7	929	6
Mean and SD	36.8 ± 18.9	979 ± 176	29.9 ± 16.8

*Subjects with abnormal pulmonary function

TABLE 2. Measurement of Inhalation Volume and Activity Deposited in the Lungs of Subjects Receiving Sulfur Colloid Aerosol with Added Albumin

Subject	Total volume inhaled (l)	Initial activity in nebulizer (MBq)	Activity deposited in lungs (MBq)
LW2*	34.5	511	22
LO	28.7	385	26
ES*	46.6	381	15
JH2	41.8	481	37
DH2	36.7	481	30
SC*	30.8	496	30
JH3	42.6	496	44
CM	45.3	370	26
KH3	37.7 (est.)	381	30
CC	36.7	389	30
RG	38.6	403	33
Mean and SD	38.2 ± 5.63	434 ± 58	29.4 ± 7.6

*Subjects with abnormal pulmonary function

As shown in Tables 1 and 2, similar volumes of the aerosol were inhaled by the two groups (36.8 l ± 18.9 l in the untreated versus 38.2 l ± 5.6 l in the HSA-treated group). Both groups also had similar lung deposition activities; i.e., 0.81 mCi ± 0.45 mCi versus 0.79 mCi ± 0.21 mCi (or 30 MBq ± 17 MBq versus 29MBq ± 8 MBq). The tables also indicate the dramatic reduction in nebulizer activity between the untreated and HSA-treated populations: 26.4 mCi ± 4.7 mCi versus 11.7 mCi ± 1.6 mCi (or 979 MBq ± 176 MBq versus 434 MBq ± 58 MBq).

During nebulization, about 1 ml of the solution became aerosolized and the remainder was retained within the apparatus. It sprayed onto the walls, and returned to the bulk solution after pressure to the nebulizer had been turned off. Activity per unit volume output was consistently between 30 and 40% of initial specific activity in the HSA-colloid experiments. (This value was less than 100% because air fed in to create the aerosol mostly carried off the water vapor generated within the nebulizer.)

No adverse reactions to either preparation were noted in healthy subjects or patients.

Comment

The change in method reported here, which does not measurably affect the size or distribution of the aerosol particles, virtually eliminates attraction between the radioisotope and the glass nebulizer, and permits reduction in the initial activity from 27 mCi (1.0 GBq) to about 12 mCi (0.4 GBq). This modified method may prove useful with other compounds, such as indium phosphate or tin colloids, utilized as aerosol agents. Further, the lower radioactivity reduces irradiation of both technologists and patients.

The addition of albumin to the sulfur colloid solution was incorporated after our initial 14 experiments regarding single photon emission computed tomography of lung aerosol deposition (results to be published). This modification, as indicated,

proved entirely satisfactory and thus has been utilized on all of our studies since its initial tests.

Acknowledgment

This work was supported by the Alberta Heritage Foundation for Medical Research and the University of Alberta Hospitals Special Services Research Fund. We acknowledge the assistance of Ms. U. Matthews, Dr. A. Noujaim, and Mr. J. Scott in reviewing and preparing this manuscript and of Ms. M. Morrison and Ms. D. Benwood for their secretarial assistance.

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