Formulation of Technetium-99m-Aerosol Colloid with Improved Delivery Efficiency for Lung Ventilation Imaging

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Static imaging of lung ventilation in multiple views or with SPECT requires a ^{99m}Tc aerosol which does not wash out during imaging. Commercially available ^{99m}Tc colloids have suitable physical properties but are inefficiently delivered from jet nebulizers. An in vitro system was used to compare the delivery of various ^{99m}Tc radiopharmaceuticals from nebulizer solutions. Delivery of noncolloidal agents (pertechnetate, pentetate, imidodiphosphate, albumin) was much greater than that of colloids. However, addition of phosphate buffer to an in-house ^{99m}Tc-tin colloid produced an agent that was delivered as efficiently as the noncolloidal tracers and which shows promise for clinical use.

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Imaging of lung ventilation is often performed with submicronic ^{99m}Tc aerosols, most commonly ^{99m}Tc-pentetate (DTPA), which washes out of the lungs at a moderate rate by absorption and this washout can give diagnostic information (*1*). However, for imaging in multiple views or using SPECT, a radiopharmaceutical which is not readily absorbed and therefore whose distribution remains virtually static would be preferable. There is a similar requirement when ventilation imaging is performed following perfusion imaging or when a radioaerosol is used to quantitate regional delivery of a therapeutic agent. Among the ^{99m}Tc radiopharmaceuticals which have been evaluated to this end are sulphide colloid (*2,3*), pyrophosphate (*4*), imidodiphosphate (*5*), and human serum albumin (*6,7*).

In evaluating these agents, we encountered the problem of poor delivery efficiency (i.e., low extent of deposition of radioactivity into the lungs) when we used sulphide colloid or tin colloid in place of imidodiphosphate, which had been used in this institution for some time but which shows definite washout during multiple-view imaging with a single-headed gamma camera.

Therefore, we designed an in vitro system to evaluate this problem and to develop an improved radiopharmaceutical for this application. It is the purpose of this paper to describe and explain our findings on delivery efficiency of the various aerosols and to indicate how we improved delivery efficiency.

MATERIALS AND METHODS

Apparatus

The in vitro system was assembled in a fume hood. The nebulizer (Mini-Neb, Trudell Medical, London, Ontario, Canada) contained 3 ml of the various radiopharmaceutical solutions (see section on radiopharmaceuticals below). Compressed air was forced through an inlet tube and the aerosol escaped through respirator tubing (22-mm diameter) and was collected in a shielded container lined with absorbant pads. The nebulizer was weighed empty and after addition of the radiopharmaceutical solution (~30 MBq diluted to 3 ml with saline). The initial radioactivity in the nebulizer was assayed in a dose calibrator. The system was then set up and compressed air was connected at a flow rate of 8–12 liter/min for 10 min, after which the weight and residual radioactivity in the nebulizer were measured.

An aliquot of 0.1 ml was removed from the liquid remaining in the nebulizer and assayed for radioactivity. From the empty, initial and residual weights, and using a liquid density of 1.0 g/ml, the initial and final volumes of liquid were determined and the percent loss in liquid volume was calculated. From the decay-corrected initial and final measurements of total radioactivity in the nebulizer, the percent loss in radioactivity from the nebulizer was calculated. The ratio of percent loss in radioactivity to percent loss in liquid volume was termed the delivery fraction.

From the measurement of radioactivity in the 0.1-ml aliquot of liquid and knowledge of the final total liquid volume and final total radioactivity, the percent recovery of radioactivity in solution was calculated. This represents the percent of the final total radioactivity in the nebulizer which is present in the liquid; initially, 100% of the radioactivity is present in the liquid. Three of the radiopharmaceuticals were also studied with an alternative nebulizer (Aero-Mist®, Cadema Medical Products, Middletown, NY), which contains a baffle and produces a smaller droplet size.

To study the behavior in solution of selected radiopharmaceuticals, the above experiment was repeated with removal and assay

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of 0.1-ml aliquots of the nebulizer solution after 2, 4 and 6 min of airflow, as well as pre- and postnebulization samples (i.e., 0 and 10 min). This produced a profile of the concentration of radioactivity in solution as a function of time. Finally, the experiment was repeated with the apparatus in the field of view of a gamma camera (ZLC 7400, Siemens Electric, Mississauga, Ontario) interfaced to a computer (PCS Plus II, Picker International, Cleveland, OH) with the following changes: the amount of radioactivity in the nebulizer was reduced to ~10 MBq to minimize camera dead-time and radiation exposure to personnel, and there was a bacterial filter (Respirgard-II, Marquest Medical Products, Englewood, CO) on the outlet of the aerosol tubing to prevent escape of radioaerosol into the room air. A series of 30 frames of 20 sec each was acquired during nebulization. Time-activity curves were generated for regions of interest placed over the nebulizer and the filter (there was negligible radioactivity in the tubing).

Radiopharmaceuticals

Pentetate, imidodiphosphate, sulphide colloid and tin colloid were prepared by addition of pertechnetate to commercial kits. Albumin was labeled by a reduction-mediated direct procedure (*8*). In-house tin colloids were prepared by addition of stannous chloride to pertechnetate solutions followed by neutralization with sodium hydroxide or phosphate buffer. Once the colloid formulation with optimal delivery properties was determined, instant kits were prepared as follows. Fifty millilters of sterile saline were placed in a sterile beaker which contained a sterile spinbar. Stannous chloride dihydrate, 20 mg in 1 ml 1 N HCl, was slowly added, followed by 10 ml 0.5 *M* phosphate buffer, pH 7.4. The solution was purged with nitrogen for 10 min, then dispensed through a sterile 0.22-μm membrane filter in 3-ml aliquots into 10-ml sterile evacuated vials. The vials were then filled with nitrogen and stored frozen until required. A thawed kit was reconstituted with 1 ml pertechnetate (2000–4000 MBq) and labeling efficiency was measured using Whatman No 1 chromatography paper developed in saline; the labeled colloid remained at the origin while radiochemical impurities migrated near the solvent front.

RESULTS

The results using the in vitro system are presented in Table 1. The values for percent loss in volume or radioactivity are not directly comparable between radiopharmaceuticals because of variability in the flow rate of compressed air. However, the delivery fractions (loss in radioactivity relative to volume) can be compared. All of the noncolloidal radiopharmaceuticals had delivery fractions greater than 0.5, while the commercially available colloids had delivery fractions of 0.12 or lower. Even sulphide colloid which had been passed through a 0.45-μm membrane filter immediately before nebulization had a delivery fraction of only 0.09. However, the in-house formulation of tin colloid buffered with phosphate was delivered as efficiently as the noncolloidal radiopharmaceuticals, while addition of phosphate buffer to the commercially available tin colloid resulted in only moderate improvement in delivery fraction. Table 1 shows that essentially the same results were obtained with the Aero-Mist® nebulizer.

A similar pattern was seen in percent recovery of residual radioactivity in solution (Table 1). Percent recovery was high (>70%) for the noncolloidal radiopharmaceuticals and the in-house tin colloid buffered with phosphate, but was very low (<15%) for the other colloids.

The time course of the concentration of radioactivity in the nebulizer solution is shown in Figure 1. For imidodiphosphate and the in-house tin colloid buffered with phosphate, concentration increased slowly during nebulization,

TABLE 1
Performance of Various Radiopharmaceuticals in In Vitro Nebulizer System

Radiopharmaceutical	%Loss		Delivery fraction	%Recovery in solution
	Volume	Radioactivity		
Pertechnetate	29.3 ± 3.5	15.4 ± 3.8	0.520 ± 0.071	110.6 ± 2.1
Pentetate	57.5 ± 4.6	39.4 ± 2.5	0.686 ± 0.018	105.9 ± 1.9
Imidodiphosphate	49.3 ± 3.4	29.7 ± 3.6	0.604 ± 0.060	86.3 ± 10.5
Albumin	61.2 ± 3.8	35.9 ± 2.3	0.587 ± 0.031	73.9 ± 9.3
Sulphide colloid	47.8 ± 9.7	4.9 ± 1.5	0.106 ± 0.041	2.4 ± 0.8
Sulphide colloid*	61.5 ± 3.3	5.4 ± 2.1	0.087 ± 0.033	3.1 ± 1.2
Sulphide colloid†	59.9 ± 5.0	5.5 ± 5.5	0.095 ± 0.091	1.9 ± 0.7
Tin colloid	64.1 ± 1.3	7.6 ± 3.4	0.118 ± 0.053	6.7 ± 5.8
Tin colloid†	58.4 ± 1.5	19.3 ± 4.3	0.323 ± 0.068	18.4 ± 2.3
In-house colloid/sodium hydroxide	51.5 ± 6.3	13.5 ± 3.6	0.267 ± 0.089	14.0 ± 10.0
In-house colloid/phosphate	46.3 ± 7.8	24.7 ± 3.4	0.542 ± 0.043	97.1 ± 6.3
Aero-Mist® nebulizer				
Imidodiphosphate	48.3 ± 5.3	30.0 ± 3.8	0.624 ± 0.063	139.4 ± 3.4
Tin colloid	46.3 ± 3.9	8.0 ± 1.2	0.172 ± 0.025	3.6 ± 1.3
In-house colloid/phosphate	57.9 ± 6.2	43.4 ± 4.5	0.753 ± 0.063	129.8 ± 6.1

Each value is mean ± s.d. for four determinations.
* Filtered through 0.45-μm membrane filter.
† Phosphate buffer added.

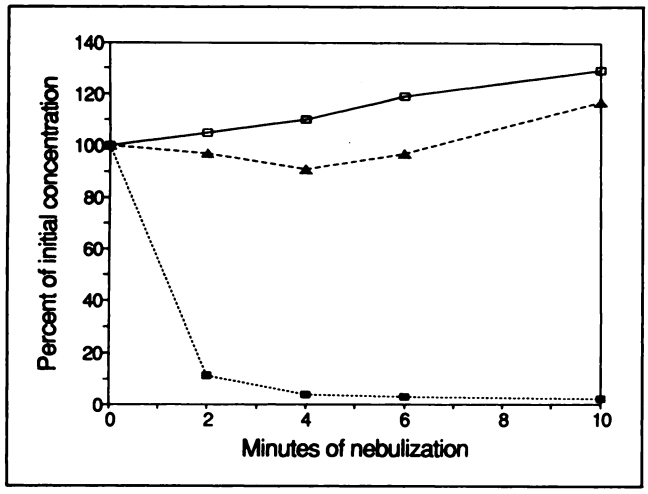

FIGURE 1. Profile of radioactivity concentration in solution during nebulization of different radiopharmaceuticals. Each value is mean of 4–6 determinations; average standard deviation (not shown) is 10%. Imidodiphosphate = □—□; sulphide colloid = ■····■; aerosol colloid = ▲——▲.

due to the greater loss in liquid volume than in radioactivity. Conversely, with sulphide colloid the concentration dropped rapidly as the colloid adhered to the walls of the nebulizer. The time profiles of delivery of radioactivity during nebulization from the gamma-camera experiments with the same three radiopharmaceuticals are shown in Figure 2. Delivery was very low and short-lived with sulphide colloid (resulting in limited total delivery with even prolonged nebulization), while imidodiphosphate and phosphate colloid produced much more sustained delivery, which leveled off with time due to inefficient nebulization of small residual volumes.

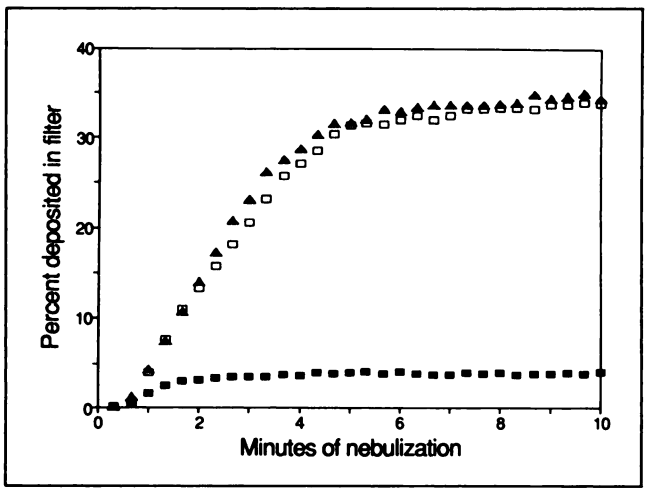

FIGURE 2. Profile of delivery of radioactivity during nebulization of different radiopharmaceuticals. Each curve represents a single experiment. Imidodiphosphate = □; sulphide colloid = ■; aerosol colloid = ▲.

DISCUSSION

Of the ^{99m}Tc radiopharmaceuticals which have been reported for static imaging of lung ventilation, only sulphide colloid and human serum albumin show negligible washout over the time required for multiple views with a single-headed gamma camera. However, we have noted poor delivery efficiency of colloids, necessitating either a large quantity of radioactivity in the nebulizer, which can result in excess exposure to personnel, or prolonged ventilation times, which are undesirable in compromised patients, although even prolonged nebulization increases total delivery only marginally. We therefore looked for a way to improve the delivery efficiency of colloids.

The in vitro system allowed quantification of the delivery of radioactivity and liquid volume from the nebulizer. With all the radiopharmaceuticals studied, the loss in radioactivity was less than the loss in liquid volume (i.e., delivery fraction was <1), largely due to evaporation of water (*9–11*). However, for the noncolloidal radiopharmaceuticals, delivery fraction was greater than 0.5 whereas delivery fraction was 0.12 or lower for the commercially available colloids (Table 1).

One possible explanation for the poor delivery of colloids is that the diameter of the colloid is too large relative to the diameter of the aerosol droplets. However, removal of larger colloids by passage of sulphide colloid through a 0.45-μm membrane filter (which removed about one-half of the radioactivity) did not improve the delivery fraction (Table 1). Moreover, there was little difference between the Mini-Neb and Aero-Mist® nebulizers; if diameter were the determining factor, there should have been greater delivery of sulphide colloid from the Mini-Neb nebulizer than from the Aero-Mist® nebulizer.

A delivery fraction of less than one should lead to an increase in the concentration of radioactivity in the nebulizer solution as aerosol generation progresses, because the loss of liquid volume is greater than the loss of radioactivity (*9,11*). This was observed, as expected, with the noncolloidal radiopharmaceuticals, where most of the residual radioactivity was recovered in solution (Table 1 and Figure 1). However, for the colloids, the concentration of radioactivity decreased and recovery of radioactivity in solution was very low, despite minimal total delivery of radioactivity from the nebulizer. Thus, the radiocolloids appear to come out of suspension and stick to the surface of the nebulizer (Figure 1).

Additional experiments showed that this did not occur spontaneously on addition of the radiocolloid to the nebulizer, nor upon gentle bubbling with air at a flow rate insufficient to propel droplets out of the nebulizer (data not shown). However, rapid air flow may alter electric charge distributions resulting in colloids adhering to the vessel wall. This effect is well known for air currents and dust and aerosol particles in the atmosphere. Poor delivery of sulphide colloid has been noted previously (*6*).

Using an in-house tin colloid, we found that addition of

phosphate buffer prevented the loss of radioactivity onto the surface of the nebulizer and resulted in delivery fractions similar to those obtained with noncolloidal radiopharmaceuticals (Table 1). We termed this formulation the "aerosol colloid". Addition of the same buffer to a commercial tin colloid produced modest improvement in delivery fraction and recovery of radioactivity in solution (Table 1). Addition of excess phosphate buffer to sulphide colloid (which already contains phosphate buffer) did not improve delivery or recovery (Table 1).

Phosphate was evaluated because of the efficient delivery of pyrophosphate and imidodiphosphate. Indeed, we initially tried adding unlabeled imidodiphosphate to in-house ^{99m}Tc-tin colloid; this improved the delivery fraction but chromatography showed that there was also partial conversion to ^{99m}Tc-imidodiphosphate. Therefore, we selected phosphate buffer, which would not bind reduced ^{99m}Tc efficiently. It appears that phosphate prevents the tin colloid from binding to the surface of the nebulizer, possibly by impeding electric charge separations. The aerosol colloid can be conveniently prepared from an instant kit in >90% labeling efficiency.

A radioaerosol which is not cleared will result in higher radiation dosimetry to the patient than one which washes out. It has been reported that the absorbed doses to the lungs for ^{99m}Tc-pentetate and ^{99m}Tc-pyrophosphate are 1.1 and 3.1 mGy per 37 MBq initially deposited, respectively (*4*). The same study found that only 10% of the ^{99m}Tc-pyrophosphate washes out. Thus, it can be estimated that the absorbed dose from aerosol colloid would be ~3.5 mGy per study (nebulization deposits ~37 MBq). The absorbed dose from ^{99m}Tc-sulphide colloid aerosol has previously been calculated as ≤4.5 mGy per 37 MBq deposited (*12*). For comparison, 150 MBq ^{99m}Tc-macroaggregated albumin results in an absorbed dose of 8.8 mGy to the lungs (*4*).

In addition to leading to the development of an improved radiopharmaceutical formulation, this work provides further information on the behavior of colloids in nebulizer solutions. If commercial colloid kits are to be used for aerosols, it is important that the radioactivity concentration be high, so that sufficient radioactivity for imaging will be delivered to the patient within the first minute or two of nebulization, after which there is no further delivery of radioactivity because there is little radioactivity left in solution.

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