TECHNETIUM-99m-HUMAN SERUM ALBUMIN: EVALUATION OF A COMMERCIALLY PRODUCED KIT

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Results are reported on the use of a commercial kit for the labeling of human serum albumin with ^{99m}Tc. One-hour blood levels obtained in 20 subjects undergoing gated cardiac imaging were found to be 46.0 ± 10.5% (s.d.) of the administered dose. The highest labeling efficiencies (94.2 ± 9.3%) were obtained when human serum albumin 25% (salt-poor) was used. Satisfactory nuclear cardiac ventriculographic images were obtained in patients receiving the radiopharmaceutical when the labeling efficiency was at least 85%. Occasional batches were milky in appearance, contained black particulate matter, were acidic, or contained a high percentage of unbound ^{99m}Tc activity. Although this kit makes ^{99m}Tc-human serum albumin accessible to most nuclear medicine facilities for general clinical use, an active quality control program is required prior to use in patients.

Technetium-99m-human serum albumin (^{99m}Tc-HSA) is a useful blood pool radiopharmaceutical for imaging the placenta and for nuclear cardiology (*1,2*). In the past, a major obstacle to its routine use has been its complex method of preparation, requiring specialized equipment and personnel (*1*). An electrolytic method for labeling HSA with ^{99m}Tc was introduced by Benjamin (*3*). Further modification by Dworkin and Gutkowski (*4*) has led to a commercially available kit for the electrolytic preparation of ^{99m}Tc-HSA (New England Nuclear Corp., Radiopharmaceutical Division, North Billerica, Mass.) This report discusses the quality control and clinical evaluation of that kit.

MATERIALS AND METHODS

Each kit consists of (A) a sterile reaction vial containing 1 ml of 0.85 *N* hydrochloric acid and 1 μM of ferrous chloride, (B) a sterile disposable zirconium electrode, and (C) a carbonate–bicarbonate buffer solution in a 2-ml disposable glass syringe. In addition, a power supply producing a regulated current for a preset time period is employed. The human serum albumin was obtained from Hyland Labs (Costa Mesa, Calif.) as 5% HSA, or from the Massachusetts Department of Public Health (MDPH Biological Laboratories, Boston, Mass.) as 25% HSA, salt-poor. Both albumin solutions were repackaged into single-dose sterile evacuated vials using a special transfer and filter device (*5*). Technetium-99m-pertechnetate was obtained from commercial generators (Minitec Generator, E. R. Squibb & Sons, New Brunswick, N.J.; New England Nuclear Corp.).

The labeling procedure is outlined as follows:

1. Add 3–7 ml ^{99m}Tc-sodium pertechnetate to the reaction vial.
2. Add 25 mg (0.1–0.5 ml) of human serum albumin. Agitate by swirling.
3. Insert electrodes, attach power supply previously adjusted to 100 mA.
4. Invert vial, swirl gently, initiate and maintain electrolysis for 42 sec.
5. Remove electrodes and allow the reaction vial to incubate at room temperature for at least 30 min.
6. Add total contents of buffer syringe (2 ml) with gentle swirling. Vent reaction vial.

Each preparation of ^{99m}Tc-HSA was checked for particulate matter, turbidity, and pH. Labeling efficiency was determined either by descending paper chromatography with 85% methanol or by a more rapid method utilizing trichloracetic acid precipitation with membrane filtration (*6*). Twenty-four batches were assayed by both methods with com-

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TABLE 1. EFFECT OF HSA SOURCE ON ^{99m}Tc LABELING EFFICIENCY

Source	Labeling efficiency (%) Mean ± s.d.	Range
1. 5% HSA (Hyland Labs)	84.2 ± 12.4 (n = 23)	66–99
2. 5% HSA (MDPH) repackaged (frozen)	77.0 ± 20.4 (n = 25)	17–99
3. 25% HSA (MDPH) repackaged (refrigerated)	94.2 ± 9.3 (n = 135)	50.1–99

Statistical analysis—Student's t-test: 1 → 2, $0.1 < p < 0.2$; 1 → 3, $p < 0.001$; 2 → 3, $p << 0.001$.

TABLE 2. RESULTS OF QUALITY CHECKS (n = 195)

Milky solution	7 (3.5%)
Black particulate matter	31 (15.9%)
Acidic pH	3 (1.5%)

parable results. Qualitative assessment of ^{99m}Tc-HSA in humans was evaluated in over 150 patients referred for gated cardiac scanning. Twenty of these patients had blood samples drawn 1 hr after intravenous administration and the fraction of administered radiopharmaceutical present in the blood volume (7% body weight) was calculated using whole blood.

RESULTS

The variation in labeling efficiency obtained with different sources of albumin is illustrated in Table 1. The highest labeling efficiency (94.2 ± 9.3%) was obtained when 25% human serum albumin (salt-poor) was used. By Student's t-test this is significantly different from 5% HSA ($p < 0.001$), although there is not a significant difference between frozen and nonfrozen 5% HSA at the 95% confidence level. Milky appearance resulting in an inability to filter the solution, black particulate contamination, and acidic pH values were observed in several preparations (Table 2). The average ^{99m}Tc-HSA 1-hr blood level in 20 patients was 46.0 ± 10.5%. Satisfactory cardiac images were obtained up to 5 hr after labeling. During this period there was no increase in unbound ^{99m}Tc activity as determined by in vitro methods. Unsatisfactory images were obtained, however, in patients who received ^{99m}Tc-HSA with an initial labeling efficiency of less than 85%. This group represented 16% of the patients studied.

DISCUSSION

The electrolytic method of labeling human serum albumin with ^{99m}Tc has proven satisfactory with the commercial kit used in this study. However, a rigorous quality check of this radiopharmaceutical must be carried out prior to administration. This check includes visual inspection for turbidity and particulate matter, pH determination, and radioassay for labeling efficiency.

Visual inspection of the final product should show a clear or slightly opalescent fluid. Although it is not certain what causes the occasional milky appearance, such batches would not readily pass through a 0.22-micron or 0.45-micron membrane filter and were rejected. The presence of black particulate matter is possibly a result of the formation on the electrode of nonstoichiometric hydrides of zirconium. The voltage at which the electrolysis takes place is sufficient to generate a significant quantity of hydrogen which is very likely absorbed by the zirconium to form the greyish-black solid (7). Evolution of the gas causes these deposits to flake. Because of a 16% incidence of particulate matter contamination, a routine filtering of each batch through a 0.22- or 0.45-micron membrane filter is required prior to administration. An occasional low pH value (pH 1–2) was caused by inefficient buffering. In at least one such instance crystalline material was observed at the hub of the buffer syringe.

A 25% solution of HSA (salt-poor) yielded the highest labeling efficiency. Factors other than the albumin may contribute to variation in labeling efficiency. These include possible procedural variability in our preparation as well as variability between sources of the kit. The potential deleterious effect of increased molar concentrations of ^{99}Tc in gen-

TABLE 3. COMPARISON OF BLOOD LEVELS OF RADIOLABELED HSA

Agent and reference	% Administered dose in blood volume (7% body weight)	Comments
^{131}I-HSA (1)	38*	1-hr level in mice
^{99m}Tc-HSA (Fe–ascorbic acid) (1)	32*	1-hr level in mice
^{99m}Tc-HSA (electrolytic kit) (7)	35.1 –47.6	30-min level in mice
^{99m}Tc-HSA (electrolytic kit) (†)	46.0 ± 10.5	1-hr level in man

* Taken from graph.
† Authors' current data.

erator eluates (*8,9*) that have not been eluted within the past 24 hr is also to be considered. The variability in labeling efficiency demands that each batch be assayed prior to patient administration.

The albumin used in this study was repackaged into a single-dose vial which was subsequently stored under refrigeration until needed. This served to decrease the cost of the albumin and minimize the risk of bacterial contamination from repeated entries into a large-volume container.

The 1-hr whole-blood levels of 46.0 ± 10.5% were similar to those reported in animals using ^{131}I-human serum albumin and ^{99m}Tc-HSA prepared by both the electrolytic and iron ascorbate methods (Table 3) (*1,10*). This blood level routinely produced sufficient radioactivity to provide high-quality cardiac blood pool images.

The availability of this kit should provide a useful radiopharmaceutical for general clinical use. The quality control described, however, is mandatory prior to patient administration.

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