Effects of Multiple Factors on the Stability of New Technetium-99m Labeled Radiopharmaceuticals: MAG_3, Cardiolite, and CardioTec

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During transport, radiopharmaceuticals may break down in radiochemical purity and stability due to various physical conditions. In this study, I examined the effects of air, temperature changes, agitation, and time on technetium-99m (^{99m}Tc) mertiatide (MAG_3) (Mallinckrodt Medical, St Louis, MO), ^{99m}Tc sestamibi (Cardiolite) (Du Pont Radiopharmaceuticals, N. Billerica, MA), and ^{99m}Tc teboroxime (CardioTec) (Squibb Diagnostics, Princeton, NJ). Samples of each radiopharmaceutical were subjected to air, high and low temperatures, and agitation in simulated conditions. Quality control procedures were performed on the test samples at different time intervals to determine each radiopharmaceutical's radiochemical purity and stability. All of the radiopharmaceuticals remained at least 90% radiochemically pure, under all of the conditions. This study demonstrates that MAG_3, Cardiolite, and CardioTec remained stable and radiochemically pure under various physical conditions that might be encountered during transport from a commercial nuclear pharmacy.

Technetium-99m (^{99m}Tc) labeled radiopharmaceuticals can undergo a reduction in radiochemical purity and stability from the time the materials are prepared at a commercial radiopharmacy until their administration for patient studies. Certain conditions can effect the radiopharmaceuticals during transportation or in the clinic, such as, air in the vial or syringe, agitation, temperature changes, or time exceeding the manufacturers' suggested expiration time.

Previous studies done on the effects on radiopharmaceutical stability and the factors influencing stability have shown that ^{99m}Tc-labeled radiopharmaceuticals are relatively stable under a wide range of conditions and do not break down easily (*1–3*). This study will address the effects of the aforementioned conditions on several newly developed ^{99m}Tc-labeled radiopharmaceuticals.

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MATERIALS AND METHODS

The radiopharmaceuticals evaluated were MAG_3, Cardiolite, and CardioTec. The radiopharmaceuticals were obtained in lyophilized preparations and were prepared according to the manufacturers' package inserts. Approximately 150 mCi of sodium pertechnetate was injected into each kit. Normal saline was added to bring the volume of each kit to approximately 3 ml. One-tenth ml samples from each kit were drawn in 1-cc syringes and were subjected to various conditions: agitation, high and low temperatures, air entering the syringe, and time lapse greater than the manufacturers' suggested time limit (6 hr) before use.

The effect of agitation was tested on five samples of each radiopharmaceutical, by placing the samples on an aliquot mixer in large test tubes, supported in a sponge for 30 min. Temperatures above room temperature were obtained by placing five samples of each radiopharmaceutical in sealed syringes in a rack and placing the rack into a water bath heated to 36°C–38°C for 30 min. Temperatures below room temperature were obtained by refrigerating five samples of each radiopharmaceutical for 30 min at 7°C–10°C. The effect of air in the syringe was obtained by drawing an air bubble of approximately 0.5 cc into each syringe, shaking the sample down to the hub of the syringe, then drawing the syringe back to the 1-cc mark. The samples were exposed to air for 1 hr, and then the air was removed.

MAG_3

The effects on the radiopharmaceuticals' radiochemical purity and stability were tested, using the manufacturers' recommended quality control procedures. MAG_3 was tested by liquid chromatography using a reverse phase, solid phase extraction cartridge. The cartridge was prepared by first flushing it with 10 cc of pure ethanol and then flushing it with 10 cc of 0.001 N hydrochloric acid. The cartridge was drained by flushing it with 5 cc of air. Then a 0.1 cc sample of MAG_3 was applied to the cartridge. Ten cc of 0.001 N hydrochloric acid was pushed through the cartridge and collected in a culture tube for counting. The cartridge was eluted again with 10 cc of 1:1 ethanol:saline solution and collected in a second

culture tube for counting. All elutions of the cartridge were performed in a dropwise manner (30–40 μl increments) using a 10 cc syringe. The cartridge was placed in a third tube for counting. The sample elutions and the cartridge were counted in a dose calibrator.

The first sample was a measurement of the amount of free pertechnetate and a fraction of hydrolyzed reduced technetium present in the sample. The second elution contained the amount of tagged radiopharmaceutical, while the cartridge contained the remaining hydrolyzed reduced technetium and nonelutable impurities. The percentages of tagged complex and impurities present were calculated as follows:

$$\text{Percent } ^{99m}\text{Tc-MAG}_3 = \frac{\text{activity of 2nd fraction}}{\text{total activity of all 3 fractions}} \times 100\%$$

$$\text{Percent hydrophilic impurities} = \frac{\text{activity of 1st fraction}}{\text{total activity of all 3 fractions}} \times 100\%$$

$$\text{Percent nonelutable impurities} = \frac{\text{activity of cartridge}}{\text{total activity of all 3 fractions}} \times 100\%$$

Cardiolite

Cardiolite was tested for radiochemical purity and stability by Baker-flex aluminum-oxide thin-layer chromatography (TLC). One large drop of ethanol was placed 1.5 cm from the bottom of a Baker-flex aluminum-oxide coated, pre-dried, plastic 2.5 cm × 7.5 cm TLC plate. Two small drops of Cardiolite test sample were placed side by side on the ethanol spot before the spot could dry. The plate was then placed in a desiccator and allowed to dry for 15 min. The TLC plate was placed in a test tube with 3 to 4 mm ethanol and allowed to equilibrate for 10 min. The TLC plate was cut 4 cm from the bottom and the activity was measured in a pulse-height analyzer with a window setting of 60 to 140 keV. The percentage of tagged complex was calculated as follows.

$$\text{Percent } ^{99m}\text{Tc sestamibi} = \frac{\mu\text{Ci top fraction}}{\mu\text{Ci both fractions}} \times 100\%$$

CardioTec

To test the radiochemical purity of CardioTec, paper chromatography was employed. This method required 0.9% sodium chloride and acetone as solvents and Whatman 31 ET chromatography strips. Two strips, ~11 cm in length, were spotted with the radiopharmaceutical, 2 cm from the bottom. The strips were placed in the appropriate solvent and were removed when the solvent front reached 2 cm from the top of the strip.

One strip was placed in a 1:1 solution of NaCl:acetone and was then divided after it dried, at a point 4 cm from the bottom. This was done to measure the hydrolyzed reduced fraction. The second strip was placed in a 0.9% NaCl solution, removed at the appropriate time, dried, and divided at the 6.5-cm mark. This measured the amount of soluble contaminants in the sample. The percent bound, percent free pertechnetate, and percent hydrolyzed reduced was calculated as follows.

$$\text{Percent hydrolyzed reduced } ^{99m}\text{Tc (\%A)} = \frac{\text{activity of bottom segment}}{\text{activity of top + bottom segment}} \times 100$$

$$\text{Percent soluble contaminants (\%B)} = \frac{\text{activity of top segment}}{\text{activity of top + bottom segment}} \times 100$$

$$\text{Percent radiochemical purity} = 100\% - (\%A + \%B)$$

RESULTS

With the cartridge quality control method, MAG_3 was found to remain 96.0% pure bound compound when subjected to air and high and low temperatures for 30 min and to agitation for 1 hr. Table 1 shows the results of testing on the MAG_3 samples. The effect of agitation on the MAG_3 samples was slightly higher than the effects of the other test variables (temperature changes and air).

Table 2 shows the results of testing on the Cardiolite samples. Cardiolite remained most stable under cold conditions, with 99.1% of the compound remaining bound to the technetium pertechnetate, as demonstrated by quality control procedures. Air had the greatest effect on the samples, but the Cardiolite remained 92.0% pure bound compound. Heat and agitation resulted in the samples remaining 95.4% and 97.9% pure bound compound, respectively.

Table 3 shows the results of testing on the CardioTec samples. After paper chromatography was performed on the CardioTec test samples, it was determined that the samples remained most stable during agitation. Air in the sample syringe had the greatest effect; 91.0% pure bound compound after 1 hr.

The effects of time lapse of each radiopharmaceutical is shown in Table 4.

DISCUSSION

The radiopharmaceuticals used in this study were chosen because they are new to diagnostic nuclear medicine imaging. MAG_3 is a new radiopharmaceutical developed for renal scintigraphy, which is gaining wide acceptance in clinical practice (*4*). Cardiolite is a newly developed ^{99m}Tc isonitrile, which can be used for simultaneous evaluation of ventricular function and myocardial perfusion (*5*). CardioTec is a boronic acid adduct of technetium dioxime that is used for myocardial perfusion imaging (*6*).

Regardless of transportation guidelines, technetium-labeled radiopharmaceuticals may become unstable during transportation or in the clinical setting. All ^{99m}Tc-labeled radiopharmaceuticals used in this study are required by law to be at least 90% pure bound compound (*7*). Technetium-99m labeled agents are subject to radiochemical impurities from chemical decomposition, resulting in separation of the radioactive label from the tagged compound or from radionuclidic

TABLE 1. MAG_3 Quality Control Results

Research Condition	Time (hr) Sample Tested	Percent Bound (%) of Each Sample				
		1	2	3	4	5
Heat	0.5	96.72 ± 0.74	95.68 ± 0.30	96.43 ± 0.45	95.25 ± 0.73	95.84 ± 0.14
Cold	0.5	97.44 ± 1.34	96.71 ± 0.61	95.55 ± 0.55	95.60 ± 0.50	95.19 ± 0.91
Agitation	1.0	95.85 ± 0.07	95.96 ± 0.04	95.74 ± 0.18	96.22 ± 0.30	95.84 ± 0.08
Air	1.0	95.90 ± 0.48	96.50 ± 0.12	96.96 ± 0.58	96.55 ± 0.17	96.00 ± 0.38

Each value is the mean ± s.d. of five results.

TABLE 2. Cardiolite Quality Control Results

Research Condition	Time (hr) Sample Tested	Percent Bound (%) of Each Sample				
		1	2	3	4	5
Heat	0.5	93.83 ± 1.57	95.33 ± 0.07	94.53 ± 0.87	97.76 ± 2.36	95.56 ± 0.16
Cold	0.5	99.19 ± 1.11	99.01 ± 0.93	98.89 ± 0.81	99.01 ± 0.93	99.30 ± 1.22
Agitation	0.5	97.53 ± 1.10	90.35 ± 6.08	97.79 ± 1.36	98.74 ± 2.31	97.76 ± 1.33
Air	1.0	90.15 ± 1.85	89.64 ± 2.36	96.69 ± 4.69	95.98 ± 3.98	87.57 ± 4.43

Each value is the mean ± s.d. of five results.

TABLE 3. CardioTec Quality Control Results

Research Condition	Time (hr) Sample Tested	Percent Bound (%) of Each Sample				
		1	2	3	4	5
Heat	0.5	91.2 ± 2.5	94.1 ± 0.4	97.4 ± 3.7	95.1 ± 1.4	90.9 ± 2.8
Cold	0.5	92.2 ± 4.0	98.7 ± 3.5	99.7 ± 4.5	91.7 ± 3.5	94.6 ± 0.6
Agitation	0.5	93.4 ± 1.3	96.2 ± 1.5	91.0 ± 3.7	94.9 ± 0.2	98.0 ± 3.3
Air	1.0	90.2 ± 1.7	92.6 ± 0.7	95.3 ± 3.4	89.9 ± 2.0	91.4 ± 0.5

Each value is the mean ± s.d. of five results.

TABLE 4. Results of Time Effects

Time Lapse (hr)	Percent Bound (%) of each Radiopharmaceutical		
	MAG_3	Cardiolite	CardioTec
0	98.8 ± 0.2	99.2 ± 0.2	99.1 ± 0.1
1	99.0 ± 0.0	99.2 ± 0.2	98.8 ± 0.2
2	98.9 ± 0.1	99.0 ± 0.1	98.5 ± 0.5
3	99.1 ± 0.4	99.1 ± 0.4	97.9 ± 0.8
6	98.3 ± 0.7	98.7 ± 1.1	95.9 ± 1.7
12	95.8 ± 0.4	96.2 ± 0.8	94.3 ± 1.1
24	94.1 ± 2.6	90.5 ± 0.6	89.9 ± 1.6

Each value is the mean ± s.d. of five results.

impurities present at the time the sodium pertechnetate is produced (*2*). Large amounts of free pertechnetate produce image artifacts in the form of stomach, thyroid, and salivary gland uptake (*2*). Any radiopharmaceutical may contain chemical, radiochemical, or radionuclidic components other than those intentionally present (*8*).

Radiochemical purity refers to the fraction of a specific radioisotope that is present in the desired chemical form (*8*). Radiochemical impurities may alter the critical organ dose, change biodistribution, and lead to image quality degradation (*2*). The presence of radiochemical impurities would rarely produce a serious toxic reaction but could lead to misdiagnosis of a patient by the nuclear medicine physician (*8*).

CONCLUSION

This study demonstrates that the stability of MAG_3, Cardiolite, and CardioTec, under average transport conditions, is comparable to that of conventional technetium imaging agents. If care is taken during preparation, and if transportation guidelines are followed carefully, MAG_3, Cardiolite, and CardioTec remain radiochemically pure and stable from the time of preparation at commercial laboratories until they are used in the clinical setting.

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