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Testing Different Storage Conditions for ^{99m}Tc-MAG3 Kit: Can Hot Fractioning Reduce the Cost per Unit Dose?

Pınar Özgen Kıratlı, MD; and Bilge Volkan Salancı, MD

Department of Nuclear Medicine, Hacettepe University Medical Center, Ankara, Turkey

Since its release for routine clinical use, ^{99m}Tc-mercaptoacetyltriglycine (MAG3) has become an important alternative to ^{131}I-labeled orthoiodohippuran. The cold kit for MAG3 is expensive, especially in developing countries. Therefore, unique storage conditions should be provided for cost reduction. Cold fractioning is a well-known procedure but has special requirements, such as a nitrogen tank and a laminar flow hood. The aim of this study was to prolong the shelf life of ^{99m}Tc-labeled MAG3 by a hot fractioning method, which separates the patient doses after ^{99m}Tc labeling. The radiochemical purity of the ^{99m}Tc-labeled MAG3 kit was tested under different storage conditions. Hot fractioning of the ^{99m}Tc-labeled MAG3 kit was found to be a possible alternative to cold fractioning for routine clinical studies.

Key Words: ^{99m}Tc-MAG3, cost reduction; fractioning

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Since 1986, ^{99m}Tc-MAG3 has been in routine clinical use (*1*). The better physical properties of ^{99m}Tc on image quality and the lower patient dose have made ^{99m}Tc-labeled MAG3 a preferred alternative to ^{131}I-hippuran in the evaluation of renal tubular function. However, the cold kit for MAG3 is quite expensive worldwide, especially in tertiary countries. The physical shelf life of ^{99m}Tc-labeled MAG3 is quite short (4 h), and gamma camera dynamics limit the number of patients for renal scanning. These factors also restrict the effective use of the labeled kit and increase the cost per unit dose.

Cold kit fractioning and improvement of storage conditions after labeling are common methods for cost reduction of MAG3 (*1*). A longer shelf life after labeling with ^{99m}Tc increases the number of renal studies that can be performed.

The objective of this study was to present a simple alternative procedure, which we term *hot fractioning*, to reduce the expense of the MAG3 kit (ROTOP).

MATERIALS AND METHODS

^{99m}Tc was obtained from a 16-GBq generator (Elumatic III; CIS Bio International) and was tested for the presence of aluminum ion by a Tec-Control system (Biodex Medical) and ^{99m}Mo breakthrough.

The MAG3 kit was labeled with ^{99m}Tc by following the instructions on the ROTOP MAG3 package insert. A maximum dose of 2,500 MBq of ^{99m}Tc in a 2-mL volume was used for labeling. The MAG3 kit from ROTOP does not require heating, which is a critical step in the transchelation process for preparation. The kit formulation contains 2 vials. Vial 1 comprises 0.20 mg of MAG3, 0.06 mg of zinc (II) chloride dihydrate, and 22 mg of dinatrium tartrate dihydrate. Vial 2, 2.5 mL of sodium phosphate buffer solution, comprises 14.4 mg of sodium monohydrogen phosphate dihydrate, 2.65 mg of sodium dihydrogen phosphate monohydrate, and 1 mL of water. Ten minutes after the ^{99m}Tc and MAG3 were mixed, 2 mL of buffer solution were added. The final solution was incubated another 10 min at room temperature (24°C).

To test different storage conditions, 3 groups of samples (groups A, B, and C) were prepared. Each sample contained 0.2 mL of ^{99m}Tc-MAG3 solution. The samples were taken by gauge syringes after labeling with ^{99m}Tc and were stored in the dark at different storage temperatures. Group A was stored at room temperature, group B at 4°C, and group C at −20°C. Each group consisted of 1 sample for each of 4 different intervals: 0, 5, 8, and 24 h.

Radiochemical purity (RCP) was determined by thin-layer chromatography (TLC) at 0, 5, 8, and 24 h for each group, and the results were compared with 0-h RCP values. At least 2 TLC tests were performed for every sample. Samples of groups B and C were left at room temperature for 5–10 min before RCP testing. For RCP testing, a 2-strip TLC method was used for all groups. In this method, one 10 × 1 cm instant TLC-silica gel (ITLC-SG) strip was developed in methylethylketone:acetoacetate solution (2:3)

For correspondence or reprints contact: Pınar Özgen Kıratlı, MD, Department of Nuclear Medicine, Hacettepe University Medical Center, 06100 Sıhhıye, Ankara, Turkey.
E-mail: pkiratli@hacettepe.edu.tr

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to a distance of 8–10 cm, and a second strip was developed in acetonitrile:water solution (1:1). Additionally, a mini-strip Tec-Control system was used for these groups. In this method, an ITLC-SG strip was developed in chloroform: tetrahydrofurane (3:2) and acetone. RCP results that had binding ratios lower than 90% were considered invalid.

RESULTS

RCP Results for Group A. Samples taken after labeling with ^{99m}Tc were stored at room temperature. RCP testing was performed using the Tec-Control system and the 2-strip TLC method at 0, 5, 8, and 24 h. RCP testing using both methods revealed similar results. The binding ratio for 0 h was 99.7%. The mean binding ratios (±SD) at 5, 8, and 24 h were 92.1% ± 1.3%, 80.0% ± 0.85%, and 65.0% ± 4.0%, respectively.

RCP Results for Group B. These samples were stored at 4°C and incubated at room temperature for 5–10 min before RCP testing. The RCP result for 0 h was 96.6%. The mean binding ratios (±SD) at 5, 8, and 24 h were 93.9% ± 2.5%, 86.6% ± 7.8%, and 79.1% ± 7.1% with the 2-strip TLC method and the Tec-Control system.

RCP Results for Group C. The samples, which had a binding ratio of 99.2% for 0 h, were stored at −20°C and left at room temperature for 5–10 min before RCP testing. The Tec-Control system RCP results for these samples were 97.25% ± 2.48%, 97.8% ± 2.09%, and 95.5% ± 1.81% at 5, 8, and 24 h, respectively. RCP testing using the 2-strip TLC method and the Tec-Control system revealed similar results for 0, 5, 8, and 24 h.

DISCUSSION

^{99m}Tc-MAG3 was released for routine clinical use in 1986 (*1*). The ROTOP MAG3 kit is labeled with a maximum dose of 2,500 MBq (67.6 mCi) of ^{99m}Tc, allowing approximately 14 ± 3 patient doses for renal scanning. The shelf life of MAG3 after labeling with ^{99m}Tc is 4 h if stored in the dark at 2°C−8°C. The physical use of ^{99m}Tc-MAG3 and the dynamics of the gamma camera limit the number of the patients to a maximum of 7 under the best conditions. These factors also prevent the use of MAG3 in emergency nuclear medicine.

To minimize the cost of the MAG3 kit, Thorson et al. introduced the cold fractioning method and demonstrated that split doses preserve RCP stability until the 28th day (*2*). In their work, they dissolved the lyophilized ingredients of MAG3 kits with nitrogen (N_2)-purged saline, divided the solution into aliquot vials filled with N_2, and stored the final aliquots frozen at −20°C. The major problem of this method is the age of the ^{99m}Tc eluate. When aged ^{99m}Tc eluate is used for labeling, RCP values decrease significantly (*3*). Another problem that limits the use of this method is the requirement for such equipment as a vertical laminar flow hood and a nitrogen tank. This requirement increases the expense. Moreover, the preparation procedure is too complicated for use in routine studies.

We have defined a method—termed *hot fractioning*—that separates ^{99m}Tc-labeled MAG3 patient doses and stores them at −20°C to reduce the expense of the MAG3 kit, and we tested the stability of the ^{99m}Tc-MAG3 under different storage conditions after fractioning. In group A, TLC quality control testing showed that acceptable results were obtained until up to 5 h of storage at room temperature. In group B, the 2 quality control tests were concordant, and since the binding ratios were below 90% for 8 and 24 h, we take this as invalid for clinical studies. In group C, the samples were stored at −20°C and the results showed that even at 24 h the binding ratios were greater than 90%. RCP values supported the hypothesis that stability is preserved longer if ^{99m}Tc-labeled MAG3 is stored under proper conditions.

Even though TLC revealed high binding values at 24 h, because of significant radioactive decay the authors do not recommend the use of ^{99m}Tc-MAG3 that has been stored at 4°C or −20°C for 24 h. In contrast, the pharmaceutical stored at 4 h at either temperature can safely be used in the clinical work-up.

Determination of the RCP of MAG3 is a point of question. So far, 3 methods have been recommended for this purpose: high-performance liquid chromatography (HPLC), TLC, and solid-phase extraction. Free pertechnetate and ^{99m}Tc-colloid are important radioimpurities that can also be identified by TLC. HPLC has been acknowledged to yield the most sensitive results in determining the RCP of MAG3; TLC, even though it overestimates the RCP, produces results that are within acceptable limits (*4,5*) and is still a valuable tool in most institutions.

After labeling with ^{99m}Tc, MAG3 has a longer shelf life that permits use in more patients, even patients being treated in the emergency room. Therefore, proper storage conditions are important for decreasing the cost per unit dose. A shelf life of 4–5 h can be obtained when the instructions of the MAG3 kit are followed. Prolongation of the shelf life to 8 h or even 24 h is possible. Although the RCP results at 24 h were still acceptable, the administration of such ^{99m}Tc-labeled radiopharmaceuticals is not recommended because of the half-life of ^{99m}Tc (6 h). After obtaining high RCP results, we applied to some patients ^{99m}Tc-MAG3 stored at −20°C for up to 9 h, and we observed no liver uptake or thyroid gland visualization.

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CONCLUSION

We suggest that hot fractioning of the MAG3 kit (after labeling with ^{99m}Tc) allows its use until up to 8–9 h, is quite simple, and does not require specially trained personnel.

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