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Quality control of radiochemical purity and safety of 99mTc-HDP and 99mTc-phytate adiopharmaceuticals labeling

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► ***Technical note***

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ABSTRACT

Background: The use of various types of radioactive drugs has increased the usefulness of nuclear medicine. The efficiency of the labeling radioactive isotope ^{99m}Tc is crucial for the accuracy and reliability of an examination. We conducted a survey on the quality control (QC) of radioactive isotopes (RI) by measuring their purity. ***Materials and Methods:*** The QC (always or necessary) of radiopharmaceuticals was confirmed in 12 medical institutions in a metropolitan area. The radiochemical purity (RCP) of ^{99m}Tc-HDP and ^{99m}Tc-phytate was determined based on the measured radionuclide purity of ^{99m}Tc containing ^{99}Mo. In addition, the effect of time after labeling and time after elution was analyzed. ***Results:*** None of the 12 hospitals regularly performed QC, and five hospitals administered QC when necessary. The average of 30 measurements of the ^{99}Mo content in ^{99m}Tc from three manufacturers was 0.0109 for A, 0.0121 for B, and 0.0114 for C. The average labeling efficiency was 96.02% for ^{99m}Tc-HDP and 94.97% for ^{99m}Tc-phytate after labeling. The labeling efficiency of ^{99m}Tc-HDP with different times after elution was 97.56%, 95.41%, 94.86%, 93.76%, and 91.89% after 0.5, 2, 4, 6, and 8 h, respectively, and that for ^{99m}Tc-phytate was 97.21%, 97.21%, 94.42%, 93.35%, and 89.91% after 0.5, 2, 4, 6, and 8 h, respectively. ***Conclusion:*** We analyzed the degree of maintenance needed for labeling efficiency. The degree of change should be provided to the clinical practitioner as basic data for the QC of the radiopharmaceutical.

Keywords: *Quality control, ^{99m}Tc-HDP, ^{99m}Tc-phytate, labeling, nuclear medicine.*

INTRODUCTION

Nuclear medicine plays a special role in the diagnosis and treatment of the anatomical and biochemical physiology by using the specific characteristics of radioisotopes (RI) and radiopharmaceutical products. A reactor, cyclotron, or generator produces the RI. The radiation dose in nuclear medicine imaging is necessary to improve image resolution. It is better to use an RI with a relatively short half-life because of its low patient dose, but if has the disadvantage of rapid attenuation during examination. The technetinum-99m (^{99m}Tc) produced by the generator is easy to use and easy to obtain by separating the milked ^{99m}Tc from the mother nuclide molybdenum-99 (^{99}Mo) [1–3]. The ^{99m}Tc, strongly adsorbed on the alumina column in the generator, is eluted. The carrier ^{99}Tc has little effect on ^{99m}Tc labeling and radiopharmaceutical products. However, radiopharmaceuticals with monoclonal

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antibodies tend to have a reduced labeling efficiency because the amount of ligand is very small. In addition, a radiopharmaceutical used as a tracer cannot forma complex with a pharm aceutical ligand during labeling with an RI, so a reducing or stabilizing agent is needed.

The accuracy and reliability of efficient ^{99m}Tc labeling is important for developing various radiopharmaceuticals and their usefulness in nuclear medicine diagnosis [4]. Quality control (QC) of ^{99m}Tc and radiopharmaceuticals includes physicochemical purity, that is, radionuclide purity, chemical purity, radiochemical purity (RCP) of the resulting radiopharmaceuticals and biological purity, including aseptic and exothermic tests. The radionuclides and their RCP are important factors in nuclear medicine tests because they affect the quality and diagnosis of medical imaging [5, 6]. Several researchers studied the effect of the purity of ^{99m}Tc on elution and labeling.

Ahn *et al.* [7] studied the effect of radionuclide, chemical, and radiochemical purities, and, also evaluated the labeling efficiency of various radiopharmaceuticals, including methylene diphosphonic acid (MDP), dimercaptosuccinic acid (DMSA), mebro-fenin, ethyl cysteinate dimer (ECD), and mercaptocacetyltriglycine (MAG3). In addition, elution between ^{99m}Tc and ^{99}Mo was evaluated in terms of QC procedures [1, 2, 8, 9]. The presence of ^{99}Mo in the saline eluted from the generator may interfere with the labeling process and decrease the labeling yield; the radionuclide impurity also introduces an unnecessary and unacceptable additional dose to the patient [9]. Momennezhad *et al.* [9] measured ^{99}Mo contamination of the ^{99m}Tc elute from different generators over 1 year.

The aim of this study was to measure the RCP of ^{99m}Tc using a factual survey of radiopharmaceutical QC data of tertiary medical centers and analyzed the labeling efficiency of ^{99m}Tc-oxidronate (HDP) and ^{99m}Tc-phytate overtime.

MATERIALS AND METHODS

Factual survey

Factual surveys of radiopharmaceutical QC data were conducted in 12 medical institutions in a metropolitan area in South Korea.

Radionuclide purity of ^{99m}Tc

The radionuclide purity was measured by eluting ^{99m}Tc from the generator and immediately measuring its radioactivity. The radioactivity of ^{99}Mo was measured after insertion of the Moly-Shield (Pinestar Technology, Inc., Jamestowon, PA, USA) into the generator to block 100% of the ^{99m}Tc radiation (figures 1 and 2). The radionuclide purity is calculated by adding or subtracting each radioactivity with the measured background radioactivity (BKG) using the equation (1):

$$\frac{^{99}\mathrm{Mo}\,(\mu\mathrm{Ci})}{^{99m}\mathrm{Tc}\,(\mathrm{mCi})} \le \frac{0.15\,\mu\mathrm{Ci}}{\mathrm{mCi}} \qquad (1)$$

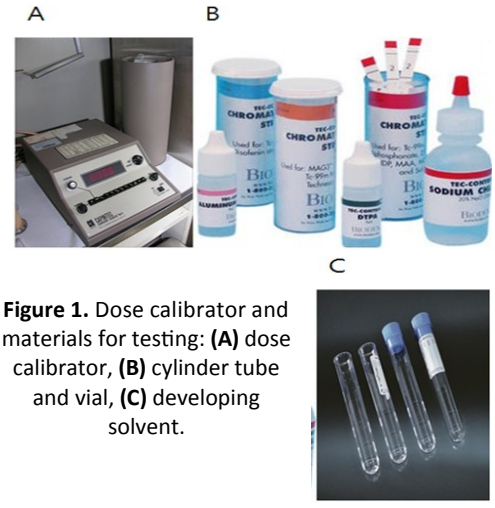

Figure 1. Dose calibrator and materials for testing: **(A)** dose calibrator, **(B)** cylinder tube and vial, **(C)** developing solvent.



Figure 2. Moly-Shield used for the radionuclide purity measurement.

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Time dependence of radiochemical purity

The radioactivity of the radiopharmaceuticals ^{99m}Tc-HDP and ^{99m}Tc-phytate from three manufacturers (A, B, and C) was measured 30 times at 0.5, 2, 4, 6, and 8 h after labeling using the time-layer-chromatography double-solvent method. After complete dissolution using instant thin-layer chromatography silica gel (ITLC-SG) chromatography paper, 3MM-Whatman chromatography paper, and developing solvent (saline and acetone) as a stationary phase, and then drying thoroughly, radioactivity was measured using a calibrator [10, 11]. Then the RCP was measured using equation (2):

$$\%TcO4\text{-}=\left[\frac{(\text{cpm of sector 2})}{(\text{cpm of sector 1})+(\text{cpm of sector 2})}\right]\times 100$$

$$\%TcO4\text{-colloid}=\left[\frac{(\text{cpm of sector 3})}{(\text{cpm of sector 3})+(\text{cpm of sector 4})}\right]\times 100 \quad (2)$$

$$\%\text{Labeling radioppharmaceutical}=100-[\%TcO4\text{-}+\%\text{Tc-colloid}]$$

Figure 3 shows procedure for measuring the RCP value using 3MM-Whatman and ITLC-SG chromatography papers.

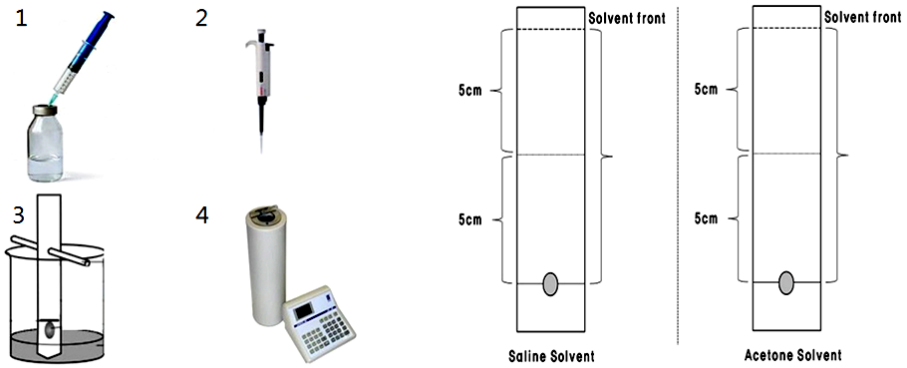

Figure3. Four steps: **(1)** place solvent intro developing vial; **(2)** spot ratiolphamaceuticals on chromatography strip; **(3)** develop strip in solvent; **(4)** count the strip using a well detector, dose calibrator or radio-chromatogram scanner, for measuring RCP using the thin-layer-chromatography double-solvent method, showing control kits and solvents.

Time dependency of ^{99m}Tc elution

^{99m}Tc was eluted from the generator at different times using the milking-system and was used to label the radiopharmaceuticals ^{99m}Tc -HDP and ^{99m}Tc-phytate. The RCP of ^{99m}Tc-HDP and ^{99m}Tc-phytate labeled at 0.5, 2, 4, 6, and 8 h after elution was measured 30 times using the same method as described above for time-dependent testing using equation (2).

Statistical analysis

Maximum and minimum values of RCP with respect to time after ^{99m}Tc-HDP and ^{99m}Tc-phytate labeling and time after ^{99m}Tc elution were measured using the IBM SPSS statistics software (ver. 19; IBM, Armonk, NY, USA).

RESULTS

Factual survey

We conducted a factual survey to confirm whether QC (always or necessary) of radopharmaceuticals was performed in 12 medical institutions with over 500 beds in the metropolitan area. No institution performed constant QC, and just five institutions performed QC only when necessary.

Radionuclide purity of ^{99m}Tc

The average radionuclide purity of ^{99}Mo in ^{99m}Tc manufacturer by A, B, and C was 0.0109 μCi (range: 0.0194–0.0091 μCi), 0.0121 μCi (range: 0.0129–0.0110 μCi), and 0.0114 μCi (range: 0.0118–0.0101 μCi), respectively. These values did not exceed the reference value for ^{99}Mo: 0.15 μCi/mCi, as shown in table 1.

Time dependence of radiochemical purity of ^{99m}Tc elution

Figure 4 (A) shows labeling efficiency of ^{99m}Tc -HDP and ^{99m}Tc-phytate with respect to time after labeling. The average labeling efficiency

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was 96.02% for ^{99m}Tc-HDP and 94.97% for ^{99m}Tc -phytate. The labeling efficiency decreased with time but all values were within the standard value. Figure 4 (B) shows the labeling efficiency of ^{99m}Tc used to label radiopharmaceuticals ^{99m}Tc-HDP and ^{99m}Tc-phytate with respect to time after elution. For ^{99m}Tc-HDP, the labeling efficiency was 97.56% at 0.5 h, 95.41% at 2 h, 94.86% at 4 h, 93.76% at 6 h, and 91.89% at 8 h, and for ^{99m}Tc-phytate, it was 97.21% at0.5 h, 97.21% at 2 h, 94.42% at 4h, 93.35% at 6 h, and 89.91% at 8 h.

Table 1. Radionuclide purity (μCi/mCi) of ^{99}Mo in 99mTc from three manufacturers.

Manufacturer	Minimum	Maximum	Average
A	0.0194	0.0091	0.0109
B	0.0129	0.0110	0.0121
C	0.0118	0.0101	0.0114

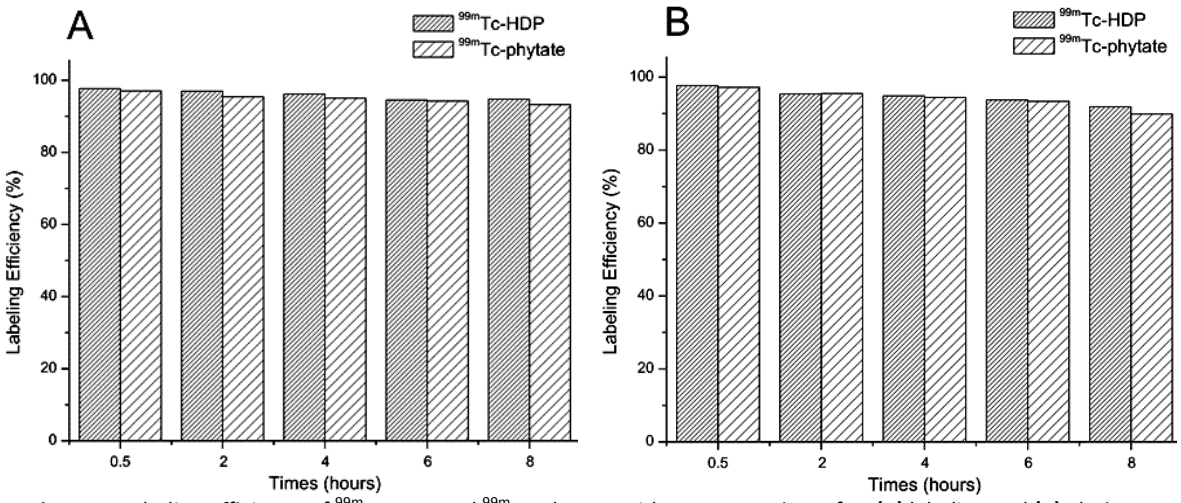

Figure 4. Labeling efficiency of ^{99m}Tc-HDP and ^{99m}Tc-phytate with respect to time after **(A)** labeling and **(B)** elution.

DISCUSSION

RI have been developed in various forms and are increasingly used as human biochemical tracers with the introduction of advanced medical devices and the development of nuclear molecular and molecular imaging [12]. Recent clinical trials have shown that radiation technologists must be aware of the correct labeling efficiency for precise examination and diagnosis. High-quality radiopharmaceuticals can be prepared that reduce distortion in nuclear imaging and ensure patient safety. Many examination errors occur because of the decline in the efficiency of radioactive labeling during nuclear medicine imaging. Therefore, it is necessary to confirm the actual condition and stability of the labeling efficiency of the radiopharmaceuticals. To verify the important of QC, we performed a factual survey and measured the radionuclide and radiochemical purities using standard methods.

According to the Korean and US Pharmacopoeias, pertechnetate (^{99m}Tc) (reference value: ~0.6-–0.7) should be <5% of the total radioactivity when 75% methanol is used as a developing solvent and the elution chromatography method is performed for ~3 h in the ^{99m}Tc purity test [13]. Kim *et al.* [8] reported that the radioactivity of ^{99}Mo was 0.02 ± 0.01 μCi which was lower than the reference value (0.15 μCi/mCi) in the 24 h the milking process. In our study, we confirmed that the radioactivity of ^{99}Mo from three manufacturers did not exceed the reference value: A: 0.0109 μCi, B: 0.0121 μCi, and C: 0.0114 μCi. In addition, Momennezhad *et al.* [9] evaluated the radionuclide impurity of ^{99m}Tc from two different generators and reported

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that ^{99}Mo contamination of the ^{99m}Tc elute was less than the maximum accepted activity limit of 0.015%. The difference between these two values may reflect different production methods the generators and different QC procedures.

The RCP varies by type. However, ^{99m}Tc-HDP used for A whole-body bone scan and ^{99m}Tc-phytate used for liver and lymphatic system examinations can be used at a labeling rate of ≥90% within 8 h, as recommended by the manufacturer and the Mayo Clinic Guidelines. In clinics, bone scans have used mainly ^{99m}Tc-HDP and ^{99m}Tc-medronic acid (MDP). An *et al.* (7) reported that the efficiency of labeling MDP with^{99m}Tc was 99.08% (average). In our study, the labeling efficiency of ^{99m}Tc-HDP was 96.2%, which is above the recommended labeling efficiency limits provided by the three manufacturers. In addition, the labeling efficiency of eluted ^{99m}Tc with respect to elapsed time was >90% for ^{99m}Tc-HDP, which is a high efficiency, and >90% for ^{99m}Tc-phytate, except for 8 h after elution, which is in the normal range for labeling efficiency. Therefore, we demonstrated that the RI can label the radiopharmaceuticals ^{99m}Tc-HDP and ^{99m}Tc-phytate within 8 h after elution from the generator based on data on safety. The limitation of our study is that we did not evaluate RCP by labeling various radiopharmaceuticals. We are considering studying these issues in the future.

CONCLUSION

The RCP of ^{99m}Tc from three manufacturers was ≤0.15 μCi/mCi, the reference value. The labeling efficiency of ^{99m}Tc-HDP and ^{99m}Tc-phytate was >90% for ≤8 h after labeling and >90% for all elapsed time after ^{99m}Tc elution. Finally, we confirmed the change in labeling efficiency and safety on the basis of results and provided basic data on setting the QC of radiopharmaceuticals in future research.

***Conflicts of interest*:** *Declared none.*

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