IMPURITIES IN ^{99m}Tc-SODIUM PERTECHNETATE PRODUCED BY METHYL-ETHYL-KETONE EXTRACTION

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In recent years there has been considerable interest in the identities and quantities of chemical as well as radioisotopic impurities in radiopharmaceutical quality ^{99m}Tc solutions (*1–3*). The presence of nonradioactive impurities in chemically significant quantities has proven especially troublesome (*4,5*) when dealing with some of the more sensitive radiopharmaceutical preparations (e.g., albumin labeling, erythrocyte labeling, sulfur colloid preparation, etc.). Radioactive impurities, especially those with appreciably long half-lives, are of concern because of their ill-defined biological behaviors and, therefore, unknown associated radiation doses.

The most widely used source of ^{99m}Tc for radiopharmaceuticals is ^{99m}Tc-sodium pertechnetate from ^{99}Mo-^{99m}Tc ion exchange generators. The most commonly encountered chemically significant contaminant in the eluate of these systems is aluminum (III), which is derived from the Al_2O_3 ion exchange column (*3,5*). This impurity is usually found in μg/ml levels. Traces of oxidizing agent are also sometimes present in generator eluates. Molybdenum-99 in μCi per 10–100 mCi of ^{99m}Tc ratios is generally found as the primary radioactive contaminant in the eluate of generators employing n,γ activated ^{99}Mo: ^{95}Zr and ^{124}Sb have recently been reported at submicrocurie levels in the eluate of such generators (*6*). Molybdenum-99, ^{103}Ru, and ^{131}I have been reported in the eluate of generators using fission-produced ^{99}Mo (*7*). Rhenium-186 was reportedly found in "instant" ^{99m}Tc-sodium pertechnetate solution (*8*).

Several radiopharmaceutical companies, and some of the larger, research-oriented hospitals have begun using methyl-ethyl-ketone (MEK) for the direct extraction of ^{99m}Tc from ^{99}Mo in 6 *N* NaOH solution (*9*). One of the primary considerations for applying MEK extraction to the production of ^{99m}Tc for radiopharmaceutical use is the improved chemical and radioisotopic purity of resulting $Na^{99m}TcO_4$ solutions (*1*). We have recently reported the results of our experience with this technique for the routine production of ^{99m}Tc (*10*).

This communication reports the levels of chemical and radioactive impurities in ^{99m}Tc-sodium pertechnetate solutions routinely produced by methyl-ethyl-ketone extraction.

EXPERIMENTAL

Sterile, pyrogen-free ^{99m}Tc-sodium pertechnetate in isotonic saline solution is prepared by MEK extraction on a daily basis in our Central Radiopharmacy (*10*). Approximately 20 ml of a MEK extracting solution is mixed with 20 ml of an alkaline (6 *N* NaOH) aqueous solution of $Na_2{}^{99}MoO_4$. Following mixing, the phases are allowed to separate and the MEK layer, containing $Na^{99m}TcO_4$, is drawn off. Residual traces of ^{99}Mo are removed by passing the ^{99m}Tc-MEK solution through a 3-cm diam $\times$ 5-cm alumina column. Following assay for ^{99m}Tc, the ketone is driven off by heating in an air stream and the dry $Na^{99m}TcO_4$ is taken up in isotonic saline. Sterilization is by Millipore filtration and/or autoclaving. We have used this technique routinely, without difficulty, for the past year.

Aluminum analysis. One-milliliter aliquots of ^{99m}Tc-sodium pertechnetate solutions were tested for aluminum content by the spectrophotometric method described by Neisler Laboratories (*11*). This method, which measures the absorbance of the aluminum (III) complex of aurin-tricarboxylic acid ("Aluminon") at 530 nm, is sensitive to 1 μg/ml.

Radioisotopic analysis. Technetium-99m was measured in a calibrated ionization chamber (Nuclear-Chicago Mediac) immediately after preparation of the sterile, pyrogen-free $Na^{99m}TcO_4$ solution.

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Molybdenum-99 was determined by gamma-ray spectroscopy at least 2 weeks after the initial ^{99m}Tc measurement. One-milliliter aliquots were taken for analysis using a well, 2-in.-diam NaI(Tl) scintillation detector and a multichannel analyzer (Baird-Atomic Model 554 Scintiscope). The area under the photopeak due to the 140-keV emission of ^{99m}Tc, which is in equilibrium with (and derived solely from) residual ^{99}Mo, was determined. A detection efficiency of 80% was assumed, the resultant activity was corrected for decay ($T_{1/2}$ = 2.8 days) and the ^{99}Mo level at the time of preparation was calculated.

Low levels of long-lived radioisotopes, which could not be measured on 1-ml aliquots of our routinely produced $Na^{99m}TcO_4$ solutions, were determined using specially extracted samples in which 300 mCi of dry ^{99m}Tc were taken up in 3 ml of isotonic saline. Spectra were taken beginning 2 weeks, and continuing for up to 2 months, after initial preparation. These spectra were used to determine the energies and half-lives of the observed gamma-ray photopeaks.

RESULTS AND DISCUSSION

Chemical impurities. Representative weekly maximum, minimum, and average concentrations of aluminum (III) in $Na^{99m}TcO_4$ solutions which were routinely produced by MEK extraction are given in Table 1. Typical values from our earlier, generator-produced $Na^{99m}TcO_4$ solutions are included for comparison*. The MEK extraction process consistently gives solutions which are lower ($\leq$2 μg/ml) in aluminum (III) content than our previous, generator-produced $Na^{99m}TcO_4$ solutions ($\cong$10 μg/ml). This is significant since it has been reported that as little as 1 μg/ml of aluminum (III) is sufficient to interfere with sensitive radiopharmaceutical preparations (*3–5*). Our MEK system rarely produces $Na^{99m}TcO_4$ solutions which exceed 2 μg/ml in aluminum (III).

Hydrogen peroxide is used in our extracting solution to insure that ^{99m}Tc is present in the extractable $Na^{99m}TcO_4$ chemical state (*9*). This oxidizing agent is rapidly converted to poorly extractable sodium peroxide upon contact with the aqueous ^{99}Mo-NaOH phase (*12*). Any extracted peroxide is ultimately decomposed during evaporation of the ketone solvent. The resulting $Na^{99m}TcO_4$ solutions are, therefore, free from chemically significant levels of peroxide.

Radioisotopic impurities. As expected, ^{99}Mo is the principal radioactive impurity in $Na^{99m}TcO_4$ produced by MEK extraction. The upper limits for ^{99}Mo in radiopharmaceutical quality ^{99m}Tc preparations are 1 μCi of ^{99}Mo/1 mCi of ^{99m}Tc with a maximum of 5 μCi of ^{99}Mo/patient dose (*13*). Table 2 gives weekly maximum, minimum, and average $^{99}Mo/^{99m}Tc$ ratios for $Na^{99m}TcO_4$ solutions which were routinely produced by MEK extraction. As before, data from typical generator-produced ^{99m}Tc are included for comparison. The extraction-produced $Na^{99m}TcO_4$ was consistently found to be significantly lower (by a factor of approximately 100) in ^{99}Mo content than ^{99m}Tc derived from our commercial generators. The level of ^{99}Mo in our MEK produced solutions is rarely found to exceed 2 ppm (relative to ^{99m}Tc).

Analyses for low levels of long-lived radioisotopic impurities were performed using initial (Monday) and terminal (Friday) extractions from several individual batches of ^{99}Mo†. Representative spectra which were obtained 3 weeks after these extractions are shown in Fig. 1. The spectra are seen to be qualitatively similar, showing a single, distinct photopeak at 600 keV‡. The half-life of this gamma-ray

TABLE 1. ALUMINUM (III) LEVELS IN $Na^{99m}TcO_4$ SOLUTIONS

Week	Aluminum (III) (μg/ml) Max.	Min.	Avg.
3–15–71*	1.3	—‡	1.0
4–12–71*	1.0	—‡	—‡
5–3–71*	—‡	—‡	—‡
8–3–70†	18	3	7
9–14–70†	23	6	9
10–26–70†	12	1	4

* MEK extraction produced.
† Ion exchange generator produced.
‡ Less than 1 μg/ml.

TABLE 2. MOLYBDENUM-99 LEVELS IN $Na^{99m}TcO_4$ SOLUTIONS

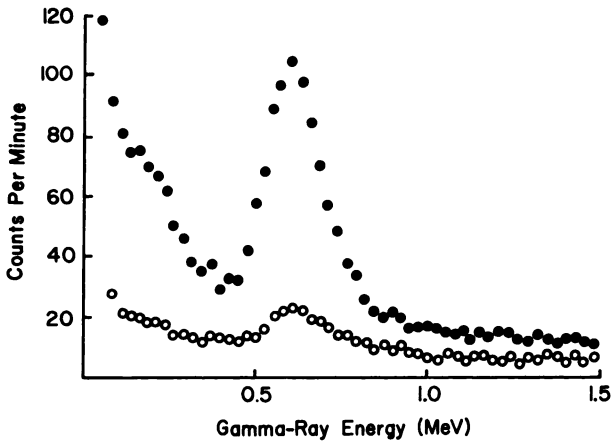
Week	$^{99}Mo/^{99m}Tc$ (ppm) Max.	Min.	Avg.
3–15–71*	1.4	0.2	0.6
4–12–71*	1.7	0.05	0.5
5–3–71*	1.4	0.1	0.8
8–3–70†	115	35	70
9–14–70†	125	95	110
10–26–70†	180	75	110

* MEK extraction produced.
† Ion exchange generator produced.

* 200 mCi "Neimotec" sterile generator.

† Target Lot Number 12: General Electric Co., Vallecitos Nuclear Center, Pleasonton, Calif. 94566.

‡ A small shoulder near 750 keV was also occasionally observed. Although the half-life of this emission could not be measured, ^{95}Zr is the most likely source of this trace impurity.



Initial Extraction (•); Terminal Extraction (o).

FIG. 1. Gamma-ray emissions of impurities in MEK-produced ^{99m}Tc.

emission was found to be approximately 60 days. On the basis of photopeak energy, half-life, and radioactive impurities known to be present in our ^{99}Mo (*14*), this photopeak was attributed to ^{124}Sb (E_γ = 603 keV; $T_{1/2}$ = 60.4 days). The relative quantities of this impurity in the various extractions suggest a moderate extraction efficiency for ^{124}Sb in this system. In all cases, this long-lived radioisotopic contaminant was found to be at the ppb (relative to ^{99m}Tc) level. This corresponds to the administration of 10^{-5} μCi of ^{124}Sb/10 mCi dose of ^{99m}Tc.

CONCLUSIONS

Chemical analysis of $Na^{99m}TcO_4$ solutions which were routinely produced by the methyl-ethyl-ketone extraction technique reveals aluminum (III) at levels averaging below 2 μg/ml. Radioisotopic analysis indicates that ^{99}Mo in ppm ratios (relative to ^{99m}Tc) is the primary source of radioactive contamination. Antimony-124 is observed in ppb ratios. These are distinctly lower levels of chemical and radioisotopic impurities than in $Na^{99m}TcO_4$ solutions produced from our previous commercial ion exchange generators.

As the requirements for chemical, radioisotopic, and radiochemical purity of radiopharmaceuticals become more stringent, individual laboratories are assuming more responsibility for quality control. This is becoming especially true with the advent of shared, community-wide, central radiopharmacy services which may undertake complete production and quality-control responsibility for short-lived radiopharmaceuticals. In such cases, methyl-ethyl-ketone extraction, or some alternative mode of routine isolation of ^{99m}Tc, may prove to offer a more efficient, less expensive means of producing $Na^{99m}TcO_4$ of significantly higher quality than that obtainable from ion exchange generator systems.

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