Determination of Radionuclide Impurities in Tc-99m: A Rapid Pulse Height Analysis Technique

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We have developed a simple and rapid procedure for determining levels of multiple radionuclide impurities in Tc-99m generator eluates before use in patients. The technique combines the use of a low gamma energy filter comprised of layers of lead, cadmium, and copper to reduce the radiation from Tc-99m—with pulse height analysis of the transmitted high energy photons from common impurities such as Ru-103, I-131, and Mo-99. The procedure, which employs a multichannel analyzer and subsequent calculations, can be performed in almost the same time required for the current technique using isotope calibrators.

Most nuclear medicine clinics analyze pertechnetate solutions for radionuclidic purity by checking for the presence of Mo-99 using a Mo-99 breakthrough shield and an isotope calibrator (*1*). This technique is adequate when Mo-99 is present at levels near the upper range of the USP XIX acceptable limit of 1 μCi of Mo-99 per mCi of Tc-99m. However, at routine contamination levels, pulse height analysis of the radiation coming from the Mo-99 breakthrough shield shows that most of the radiation is due to lead x-rays produced by the interaction of Tc-99m 140-keV gamma rays with the lead wall of the container. These x-rays as well as radiation from Mo-99 and other radionuclidic impurities are lumped together in the computation of Mo-99 breakthrough.

This lack of specificity in isotope calibrators results in certain basic analytical disadvantages. First, it does not permit clinics using fission product Mo-99 to measure USP XIX limits on [^{99m}Tc] sodium pertechnetate solution for I-131, Ru-103, or other gamma impurities (*2*). This is particularly important in clinics and radiopharmacies that use the same generator for extended periods of time by replenishing the decayed Mo-99. Under these conditions, long-lived radionuclide impurities could possibly build up in the generator in amounts exceeding the injectable limit. Radiolysis of the generator material, as well as abnormal situations such as channeling and chemical impurities in the eluant, might result in the undetected release of radioactive impurities into the pertechnetate. Second, the inclusion of lead x-rays in the computation sets a limit on the sensitivity of measurement, because this radiation is proportional to the activity of Tc-99m, not the impurities.

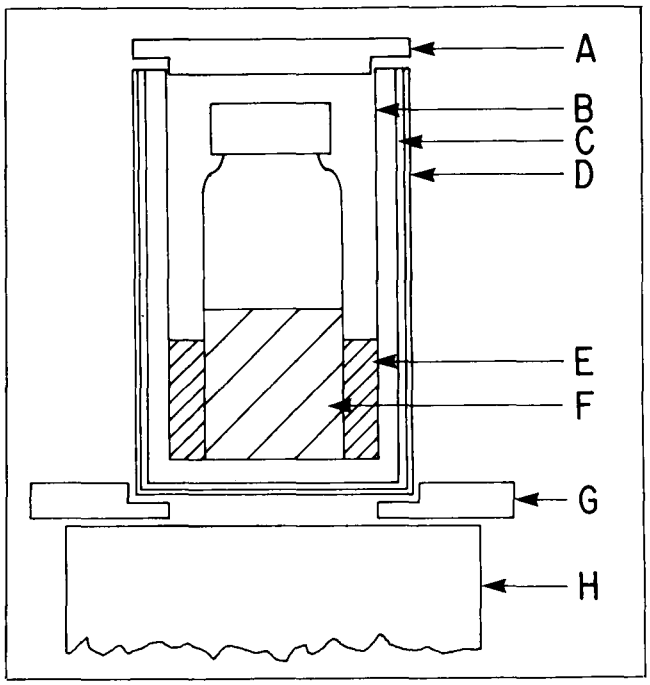

FIG. 1. Geometry of source and low energy filter relative to the detector: (A) lead cover; (B) lead layer of filter canister; (C) cadmium layer of filter canister; (D) copper layer of filter canister; (E) low density spacer (cardboard ring) to facilitate precise positioning of source in the filter canister; (F) source—10-ml serum vial containing 6 ml of solution; (G) open bottom aluminum planchet for reproducibility of filter position; and (H) NaI(Tl) scintillation detector.

Early work on the calibration of Tc-99m generator eluates described techniques to determine radionuclidic impurities. These techniques utilized NaI (Tl) detection

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and pulse height discrimination (*3*) and analysis of activity penetrating lead low energy gamma ray filters (*4*). The authors (*3*) suggested the use of a multichannel analyzer to expedite the analysis. Because single and multiple channel analyzers were mostly unavailable in nuclear medicine clinics at that time and methods using more readily available isotope calibrators were developed, pulse height analysis techniques never attained widespread routine use.

The pulse height analysis technique, which provides for high sensitivity monitoring of specific gamma impurities, has the real advantage of allowing us to follow the daily performance of a generator and monitor any trends that predict generator malfunction. More clinics now have multichannel analyzers either as independent counting entities or in conjunction with gamma cameras. Of the latter, many can be used directly for gamma spectrum analysis, while others can be adapted. We describe a simple and rapid pulse height analysis technique that provides a sensitive determination of multiple radionuclidic impurities in routine pertechnetate preparations.

Materials and Methods

Specificity and increased sensitivity were obtained with two modifications of the standard breakthrough test. The first, designed to reduce the levels of x-rays from the breakthrough shield, involved placing thin layers of cadmium and copper around the outside of the lead shield as shown in Fig. 1. The second modification eliminated the need for an ionization chamber and substituted a detector that is energy specific. While a Ge(Li) detector has superior energy resolution, we chose to use a 3 in. × 3 in. NaI(Tl) scintillation detector because of higher interaction efficiency for gammas, general availability in nuclear medicine clinics, and ease of maintenance. The detector was an integral line 3 in. × 3 in. crystal and 2-in. diameter photomultiplier tube. The Tc-99m radiation filter was positioned above the detector on a holder, fashioned to permit precise reproduction of counting geometry (Fig. 1). Pulse height spectrometry was done with a multichannel analyzer. The analyzer (Model 8100, Canberra Industries, Inc., Meridan, CT) has peak integration and energy calibration features that facilitate spectrum analysis.

Radionuclide standards used to calibrate the system were prepared by measuring high activity sources in an isotope calibrator and making accurate dilutions to obtain 6-ml sources of known activity. These sources were contained in standard 10-ml serum vials, thus replicating the counting geometry of our routine Tc-99m test sample. The Tc-99m was obtained by elution of a fission product Mo-99/Tc-99m generator.

Preliminary studies of the spectrum of generator eluants over a 3-month period revealed no photopeaks above 1 MeV; therefore, we calibrated our working baseline to 1 MeV per 512 channels. Figure 2 is an energy calibration curve obtained with sources through the low

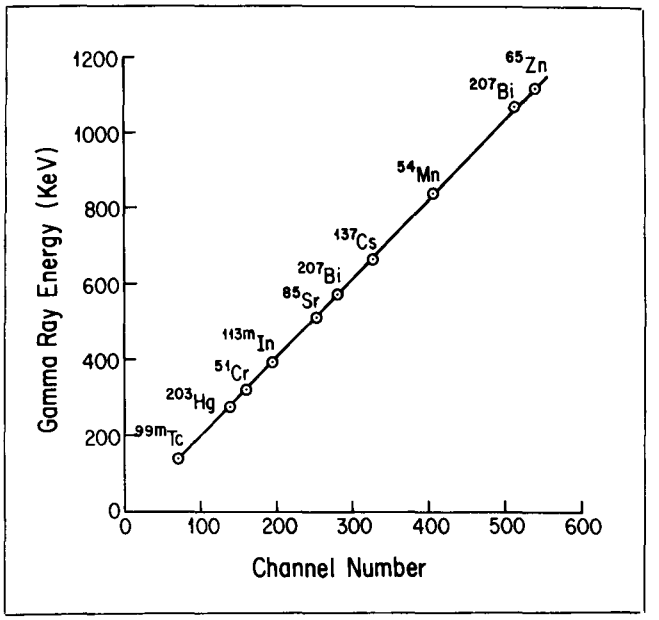

FIG. 2. Calibration curves of multichannel analyzer baseline using low energy filter.

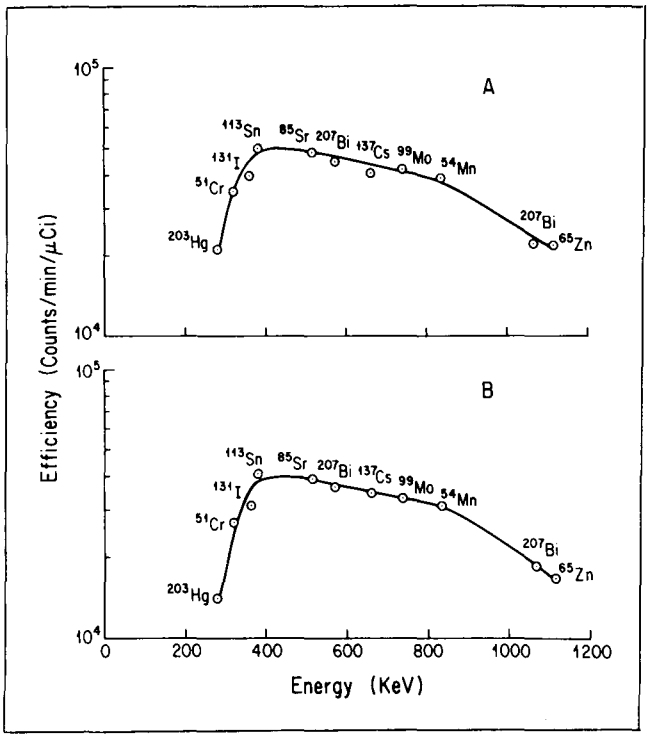

FIG. 3. Counting efficiency of system with the low energy filter. (A) count rate in the full photopeak and (B) count rate in the region of FWHM.

energy filter. Before determining the calibration curve, routine calibration checks were made prior to each analysis to ascertain that the 511-keV annihilation radiation of Na-22 was maximum in the proper channel.

Figure 3 (A and B) shows the calibration curves for the counting efficiency as a function of gamma ray energy for both the counting rate in the full photopeak and the counting rate in the full width at half maximum (FWHM),

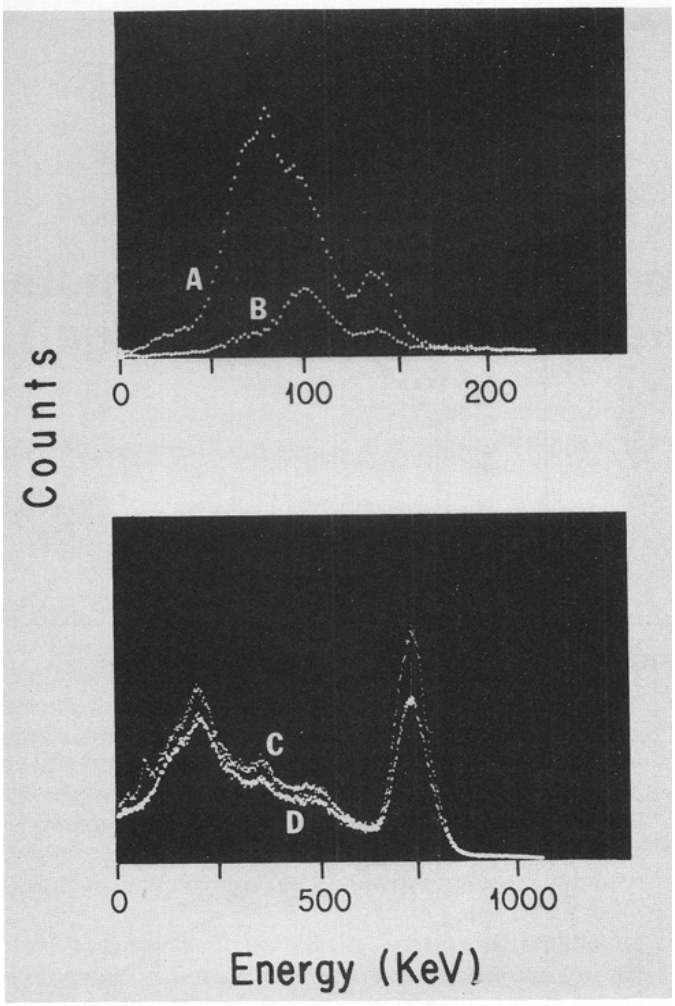

FIG. 4. (A) Spectrum of Tc-99m through lead filter without cadmium or copper layers; (B) Tc-99m through lead filter with cadmium and copper layers; (C) Spectrum of Mo-99 through lead filter without cadmium and copper layers; and (D) Spectrum of Mo-99 through lead filter with cadmium and copper layers.

respectively. To develop these curves, spectra of the standards of known activity were obtained. The counting rate in the photopeaks was corrected by subtracting background and the contribution of Compton scatter from the photopeak energy range. The contribution to the photopeak from Compton scatter was estimated by taking the average of the counting rates in the valley before and after the photopeak, and multiplying this average by the number of channels over which the photopeak count data were integrated. This estimate was based upon the assumption of a linear relationship between Compton scatter and energy within the narrow energy region of the photopeak. Counting efficiency for the photopeak was calculated from corrected counting rate and plotted against photopeak energy.

Results and Discussion

At low energy, efficiency was seen to increase sharply with increased transmission through the lead filter. Following a maximum, efficiency decreased as increasing gamma energy produced a decrease in detector interaction. The position of the low energy edge and maximum was primarily dependent upon the thickness of the lead filter, shifting to higher energy as the lead filter was made thicker. The filter thickness must be optimized to prevent excessive activity from low energy radiation (Tc-99m) with insufficient shielding or loss of sensitivity to medium energy impurities (such as I-131) with too much shielding. A filter thickness within the range of 0.15–0.3 in. of lead was found reasonable.

Figure 4 contains spectra from 125 mCi of Tc-99m and 20 μCi of Mo-99 obtained through a 0.18-in. lead filter and compares these to spectra of the same sources obtained through the lead filter with additional 0.12-in. cadmium and 0.02-in. copper layers. Use of the cadmium and copper layers resulted in a reduction of Tc-99m and Mo-99 radiation by factors of 4.5 and 1.2, respectively. Thus, in a test procedure using a device which does not employ pulse height analysis such as an isotope calibrator, it was estimated that the sensitivity for Mo-99 should increase by a factor of about 4.

When a device employing pulse height analysis is used, the ability to completely discriminate against Tc-99m radiation results in a 100–1,000-fold improvement in sensitivity. This can be seen in Table 1, which gives the lower limit for detection of some common radionuclide impurities for a 100-mCi [^{99m}Tc] pertechnetate sample using pulse height analysis and isotope calibrator techniques. Values of allowable USP XIX limits are included in the table for comparison. The limits of pulse height analysis are calculated based upon the ability to "see" peaks of approximately 10 cpm above background. The limit of analysis with this technique will readily permit the determination of any of the gamma impurities specified in USP XIX. The limit for the isotope calibrator is set by lead x-rays from the interaction of 140-keV gammas with the lead filter. Since this radiation is indistinguishable from Mo-99 when included in the Mo-99 breakthrough calculation, it places a limit on the sensitivity of 7×10^{-2} μCi/mCi of Tc-99m. This sensitivity is adequate for Mo-99 if it is the only impurity; however, it is marginal for other impurities specified in USP XIX.

TABLE 1. Sensitivity of Techniques for the Evaluation of Radionuclidic Purity in Tc-99m Radiopharmaceuticals (μCi/mCi)

Impurities	Pulse Height Analyzer Pb/Cd/Cu	Isotope Calibrator		USP XIX Acceptance Limits
		Pb	Pb/Cd/Cu	
Mo-99	7×10^{-4}	7×10^{-2}	1.5×10^{-2}	1
I-131	1×10^{-4}	—	—	5×10^{-2}
Ru-103	6×10^{-5}	—	—	5×10^{-2}

Pulse height resolution appears unchanged throughout the energy range when spectra were obtained using the lead filter. This may be seen from data summarized in Table 2.

In practice, a sample of 20 mCi or more of Tc-99m is placed in the low energy filter and a spectrum is obtained. The Compton-corrected counting rate in the photopeak is determined for each impurity as previously described and the activity-per-mCi of Tc-99m is calculated using the following formula:

$$A_i = \frac{C\gamma}{\epsilon\gamma Y A_T} \ \mu Ci/mCi \text{ of Tc-99m; where}$$

$C\gamma$ = count rate of the photopeak corrected for Compton and background (cpm);

$\epsilon\gamma$ = counting efficiency of the impurity at the photopeak (cpm/μCi);

Y = photon yield of the impurity;

A_T = activity of Tc-99m (mCi); and

A_i = activity of the impurity relative to the amount of Tc-99m (μCi/mCi).

The value for $\epsilon\gamma$ is obtained from a calibration curve and the photon yield is generally available since identity of the impurity can usually be determined from the gamma ray spectrum. Furthermore, because of the consistency of the presence of certain impurities such as I-131, Ru-103, and Mo-99, values for the constant $\epsilon\gamma Y$ can be kept on hand to facilitate calculation.

Time required to perform the test (counting and calculations) is about 5 min. This is comparable to the standard test using an isotope calibrator.

TABLE 2. Effect of Low Energy Filter on Pulse Height Resolution

Isotope	Gamma Energy keV	% FWHM	
		Low Energy Filter	No Filter
Cr-51	320	12.3	12.1
Sr-85	514	11.0	11.2
Cs-137	662	9.1	9.0
Bi-207	1064	7.2	6.9

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