Dispensing Therapeutic Amounts of Holmium-166 with a Radionuclide Calibrator

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Objective: A high-purity germanium detector (HPGe) spectrometry system was used to calibrate a radionuclide calibrator for the accurate dispensing of therapeutic amounts of ^{166}Ho to be administered to patients.

Methods: A calibrated ^{60}Co source was counted simultaneously in the same geometry as the ^{166}Ho for acquisition of gamma ray spectra. The sensitivity of the HPGe detector for the 1.379-MeV photons emitted by ^{166}Ho was determined from the 1.333-MeV photons emitted from ^{60}Co. This measured amount of ^{166}Ho was placed in an assay calibrator and the sensitivity control adjusted so that the readout matched the ^{166}Ho content.

Results: The dial setting required for the Capintec CRC-15R was found to be 748 times 10.

Conclusion: This assay of ^{166}Ho with a HPGe detector has proved useful for adjusting the sensitivity of a clinical radionuclide calibrator and can be extended to provide calibration factors for other assay calibrators used to dispense therapeutic amounts of other radionuclides used for clinical nuclear medicine procedures.

Key Words: holmium-166; radionuclide calibrator

J Nucl Med Technol 1995; 23:275–278

Holmium-166 was selected as the radionuclide of choice for a new approach to bone marrow ablation using radionuclide therapy in place of total body irradiation combined with chemotherapy (*1*). Total body irradiation is inherently limited by the radiosensitivities of the lungs and the kidneys which can only tolerate a maximum of 15 Gy (*2*). Radionuclide therapy has the potential of offering more selective dosimetry and a larger dose to the bone marrow, with a lower dose to other critical organs in the body. Holmium-166 was selected based on its shorter physical half-life ($t\frac{1}{2}$ = 26.9 hr) and emission of a high-energy beta particle (E_{max} = 1.85 MeV) that can irradiate the cavities in bone with a uniform distribution of energy and emits a small proportion of 80-keV gamma rays which permits the distribution of the administered radiopharmaceutical to be imaged in patients. The ^{166}Ho is complexed with a bone-seeking compound, DimethylDOTMP (Dow Chemical, Freeport, TX). A large fraction of this radiopharmaceutical (30 to 50%) is localized in the skeletal system, while the remainder is rapidly excreted via the urinary system. This rapid clearance minimizes the radiation absorbed dose delivered to other organs in the body, whereas the beta particles emitted from ^{166}Ho on the bone surfaces deposit a large fraction of their energy in the adjacent marrow.

Assay of ^{166}Ho presents a special challenge for a radionuclide calibrator (large ion chamber) because the beta particles produce brehmstrahlung x-rays in the stock solution which augment the signal detected from the small fraction of photons emitted (*3*). Figure 1 depicts a simplified decay scheme for ^{166}Ho (*4*). A ±10% error is the upper limit of accuracy for any radionuclide therapy assay, since the activity is designed to deliver a prescribed radiation absorbed dose to a target organ or site and both under and over dosage results in treatment failure or collateral damage. A high-purity germanium (HPGe) detector spectrometer system (Model GMX 18190, EG&G Ortech, Oakridge, TN) was used to set the sensitivity of a dose calibrator for ^{166}Ho.

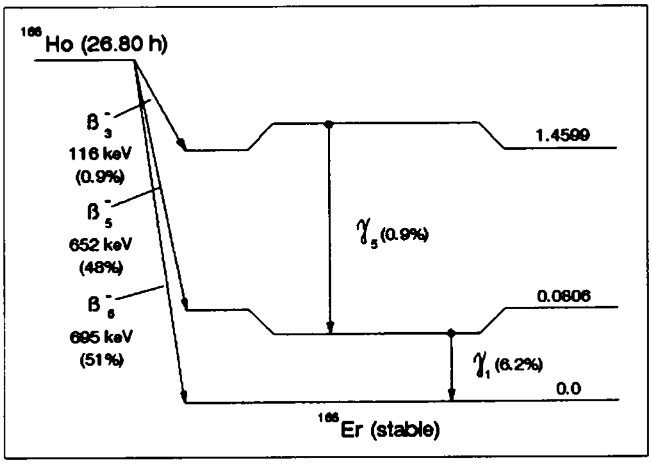

FIGURE 1. Simplified decay scheme for ^{166}Ho. The average energy of each beta particle emitted is expressed in keV. The frequency of the 81-keV and 1.379-MeV photons emitted are given as 6.2 and 0.9%, respectively.

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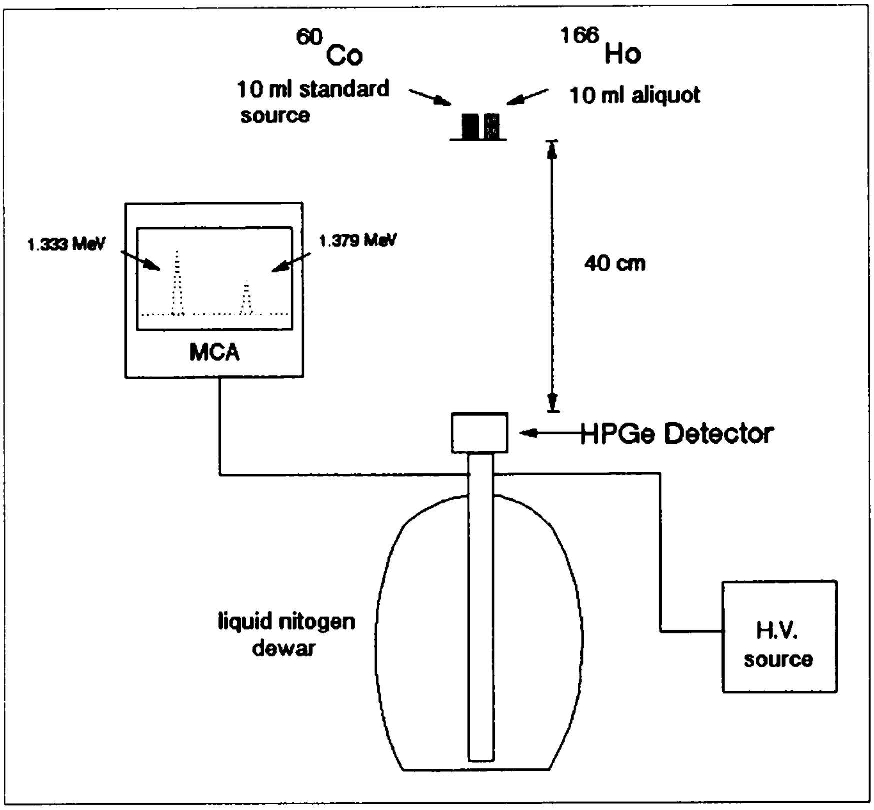

FIGURE 2. Diagram of the HPGe detector spectrometer system and location of source at 40 cm from the detector face. A 2048-channel multi-channel analyzer was used for acquisition of all spectra.

MATERIALS AND METHODS

Calibration of the HPGe Detector

A 60-cc cylindrical HPGe detector was interfaced to a multichannel analyzer (Model Series 35, Canberra Industries, Inc., Meriden, CT). The energy resolution of this detector was about 3 keV for a 1-keV per channel setting at 1333 keV. The sensitivity of the HPGe detector was determined by acquiring a spectrum of a mixed calibration source (antimony-125, tellurium-125m, europium-154 and europium-155), supplied by the National Institute of Standards and Technology (Gaithersburg, MD). This source was located at a distance of 40 cm from the surface of the HPGe detector. A large source-to-detector distance was used to reduce the effects of changes in source shape, size and errors in exact placement of the calibration source and ^{166}Ho solution. The photons emitted from a mixed radionuclide standard source ranged from 27 keV to 1596 keV. The absolute efficiency of the detector for each photon energy was determined using a region of interest and linear interpolation for subtraction of background under each peak.

Assay of Holmium-166

An aliquot approach was used for spectrometry, because the relatively large activity of ^{166}Ho dispensed for radionuclide therapy would exceed the count-rate limitations of the HPGe detector and associated electronics. A small fraction, typically 1% of the final stock solution of ^{166}Ho DOTMP, was transferred from the stock solution using a digital micropipette into a previously weighed plastic counting vial, and the weight of this sample and the stock measured to better than ±5%. The digital micropipette has a reproducibility within 5%. This ^{166}Ho sample was then diluted to 10 ml with saline. A calibrated source of 2.04 MBq (55.0 μCi) ^{60}Co was made with identical geometry and contained in a 10-ml plastic vial as the diluted ^{166}Ho aliquot was fabricated (Isotope Products Laboratories, Burbank, CA) and used to calibrate the HPGe detector.

The small aliquot of ^{166}Ho stock solution was placed adjacent to the ^{60}Co source at a distance of 40 cm in air from the surface of the HPGe detector (Figure 2). At this distance, the count rate of the detector for simultaneous acquisition of spectra from ^{60}Co and ^{166}Ho sources indicated a dead time of less than 5% on a 100-MHz multi-channel analyzer. The spectra were acquired simultaneously to reduce any errors in live-time acquisition from the different count rates encountered from each source and the significant count rate from the 49- and 81-keV photons emitted by ^{166}Ho. A spectrum was acquired for 300 sec with a gain set at 1 keV per channel (Figure 3). The number of counts detected in the 1.333-MeV photopeak from ^{60}Co, and the 1.379-MeV photopeak from ^{166}Ho, after background subtraction for each peak was used to calculate the activity of ^{166}Ho in the sample using:

$$\frac{A_{^{166}Ho}}{A_{^{60}Co}} = \frac{N_{^{166}Ho}}{N_{^{60}Co}} \cdot \frac{f_{1.333}}{f_{1.379}} \cdot \frac{\epsilon_{1.333}}{\epsilon_{1.379}} \qquad \text{Eq. 1}$$

where $A_{^{166}Ho}$, $A_{^{60}Co}$ are the activities of the aliquot of ^{166}Ho and the ^{60}Co standard source respectively, $N_{^{166}Ho}$, $N_{^{60}Co}$ are the counts detected from ^{166}Ho and ^{60}Co, respectively, $f_{1.333}$, $f_{1.379}$ are the fraction of photons emitted per disintegration from

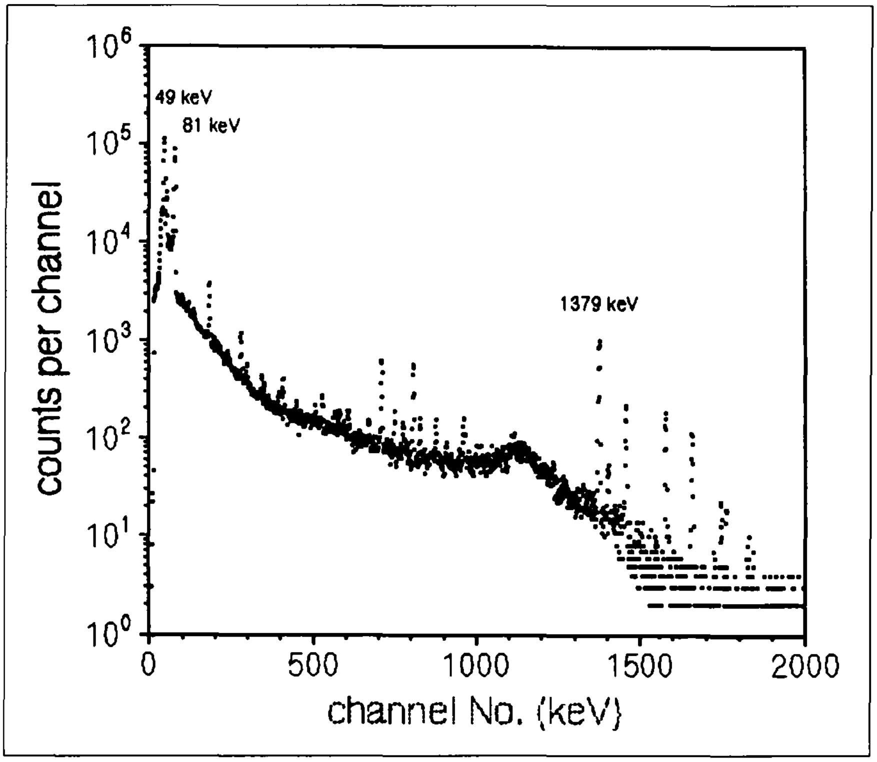

FIGURE 3. Typical HPGe spectrum acquired from ^{166}Ho. The 1.379 MeV photopeak is indicated and other prominent photopeaks detected from ^{166}Ho are at 49 and 81 keV.

^{60}Co and ^{166}Ho, respectively, and $\in_{^{166}\mathrm{Ho}}$, $\in_{^{60}\mathrm{Co}}$ are the absolute efficiency of the HPGe detector measured at 1.333 MeV and 1.379 MeV, respectively.

The absolute efficiency of the HPGe detector is considered to be the same for the 1.33-MeV and 1.379-MeV photons emitted by ^{60}Co and ^{166}Ho, respectively. The spill-down contribution of events from the 1.379-MeV photons to the 1.333-MeV peak was removed by background subtraction. A linear interpolation method was used to subtract this and the room background. The absolute detector efficiencies for the 1.333-MeV and 1.379-MeV photons were considered to be identical, since the change in sensitivity for a 46-keV difference is less than ±5%. From the measured activity of the ^{60}Co source, the activity of ^{166}Ho in the aliquot is given by:

$$A_{^{166}\mathrm{Ho}} = A_{^{60}\mathrm{Co}} \cdot \frac{N_{^{166}\mathrm{Ho}}}{N_{^{60}\mathrm{Co}}} \cdot \frac{100\%}{0.9\%}. \qquad \text{Eq. 2}$$

The concentration of ^{166}Ho in the stock solution was calculated from:

$$C_{^{166}\mathrm{Ho}} = \frac{A_{^{166}\mathrm{Ho}}}{\text{mass of aliquot}} \qquad \text{Eq. 3}$$

and the activity required for the diagnostic or each therapy study from:

$$A[\text{activity}]_{^{166}\mathrm{Ho}} = V_{\text{stock}} \cdot C_{^{166}\mathrm{Ho}} \qquad \text{Eq. 4}$$

where $C_{^{166}\mathrm{Ho}}$ is the concentration of ^{166}Ho in the stock solution in MBq/ml, V_{stock} is the volume in ml of the aliquot that was removed from the stock solution (assumed to be unit density) and A_{activity} is the activity to be administered to the patient. The volumes administered for diagnostic and therapeutic studies were typically 3 to 5 ml and could be drawn with an accuracy of better than ±5% in a 5-ml syringe.

Setting the Dose Calibrator

The measured activity of ^{166}Ho in the diluted aliquot was then placed in the radionuclide calibrator (Model CRC-15R Capintec, Inc., Ramsey, NJ) and the sensitivity of the instrument was adjusted so that the displayed reading matched the calculated activity.

Determining Therapy Dose Activity

The radionuclide calibrator was used to dispense all diagnostic and therapeutic amounts of ^{166}Ho DOTMP administered to patients enrolled in a bone marrow ablation trial. As a secondary check, the HPGe detector assay was used to compare the difference between the two instruments. The stock solution was always assayed in a 10-ml plastic vial to reduce the brehmstrahlung contribution, but otherwise always shielded in an acrylic container with a 2-cm thick wall.

RESULTS

Figure 4 illustrates the change in absolute efficiency measured for the 60-cc HPGe detector with a source located at 40-cm from the surface over the energy range 80 keV to 1.5 MeV. The radionuclide calibrator dial setting for ^{166}Ho was found to be 748 with a factor of 10. The activity of ^{166}Ho dispensed using the radionuclide calibrator was within ±10% of the activity calculated from the HPGe counts detected from

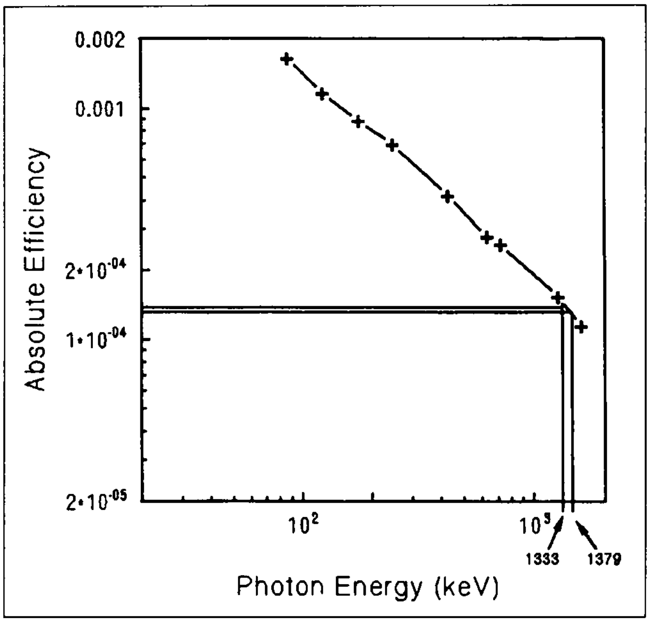

FIGURE 4. Absolute efficiency of the HPGe detector efficiency measured with a calibrated NIST mixed radionuclide standard source located at a source-to-detector distance of 40 cm in air.

the aliquot corrected for the total volume of the stock solution administered to each patient (Table 1).

The response of the radionuclide calibrator to ^{166}Ho as a function of source volume and within-chamber displacement was measured and found to be similar to the usual characteristics described for routine diagnostic radionuclides.

DISCUSSION

This study describes a method that can be used for the accurate measurement of ^{166}Ho for administration to patients receiving radionuclide therapy. Our results show that an HPGe spectrometer system can be used to calibrate a commercially available radionuclide calibrator widely used in clinical nuclear medicine. The radionuclide calibrator can then be used to dispense relatively large activities of ^{166}Ho. The optimum setting for assay of ^{166}Ho was found to be 748. The readout value must be multiplied by 10.

TABLE 1
Comparison of the Assay of ^{166}Ho*

Volume administered (ml)	HPGe activity (GBq)	Radionuclide calibrator activity (GBq)	HPGe-CRC15R (% difference ±)
5	10.9	11.1	1.8
5.3	10.2	10.4	1.9
5	9.58	10.3	7.3
5	34.3	32.7	4.7
5.4	8.49	8.77	3.5
10	16.9	17.1	1.2

*Holmium-166 dispensed for six therapeutic patients using the radionuclide calibrator with the total activity calculated from the counts detected with the HPGe spectrometer.

The response of an ion chamber system, for the assay of a radionuclide such as ^{166}Ho, is complicated by many factors such as source volume, containment, location, energy of the photons emitted, etc. The relatively small fraction of brehmstrahlung photons emitted by interaction of the beta particles emitted by ^{166}Ho with the atoms in the stock solution and the plastic wall of the container is a problem, primarily because ^{166}Ho emits a small proportion of photons per disintegration. For radionuclides such as ^{131}I, which also emit beta particles and photons, this brehmstrahlung contribution from beta particle interactions represents an insignificant fraction of the total response of an ion chamber to small sources located in the well.

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