The Use of Positron Emitters to Evaluate Linearity of Radionuclide Dose Calibrators

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Objective: Four positron emitters, ^{18}F, ^{13}N, ^{11}C and ^{15}O, were studied immediately after production for possible radionuclidic contaminants.

Methods: A series of activity measurements was performed with a dose calibrator over decay periods of 20 half-lives for each radionuclide. Individual semilogarithmic time-activity curves were generated over a wide range of activities (from a few hundred MBq to the 370 kBq (10 μCi) level). The presence of radionuclidic contaminants in activity measurements over reasonably long periods will manifest as deviations from linearity in these plot presentations.

Results: Nitrogen-13 samples showed significant deviation from linear response even at the MBq level due to the presence of a ^{18}F contaminant. However, ^{18}F, ^{11}C and ^{15}O samples showed a virtually linear response over the entire activity range.

Conclusions: Although most of these positron emitters maintain the linear decay characteristics in the practical use range, investigators should be aware of the increasing contribution of long-lived contaminants in the low end of the activity range. Although the 2-min half-life of ^{15}O might be sufficient to allow performance of linearity measurements within minutes, we feel that ^{11}C might be an ideal positron emitter to accomplish this task due to its more practical half-life period.

Key Words: Fluorine-18, nitrogen-13, carbon-11, oxygen-15, radionuclide contaminants, dose calibrator.

J Nucl Med Technol 1994; 22:74–78

PET is one of the more unique medical imaging modalities currently being used for clinical and research studies. Quantitative three-dimensional images of specific biochemical, physiological and pathophysiological processes can be obtained by this technique using radiopharmaceuticals labeled with positron-emitting radionuclides, such as ^{13}N, ^{11}C and ^{15}O (*1*). The most common PET radionuclide is ^{18}F, a chemical substitute for hydroxyl groups in organic molecules.

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PET has been used to assess myocardial viability, brain disorders such as epilepsy, Parkinson's disease, Alzheimer disease, stroke, etc., as well as tumor function (*2,3*). These studies provide high-quality images with relatively low radiation doses to the patient and are generally superior to those produced by SPECT. The synthesis of PET radiopharmaceuticals is commonly monitored by radionuclide dose calibrators placed inside "hot cells" which are lead-lined fume hoods with clear lead-glass windows for viewing purposes. For accurate measurements of activities of positron emitters, the use of an appropriately calibrated dose calibrator is essential. For reliable measurements of the radionuclidic contaminants in the obtained positron emitters, the dose calibrator is checked for constancy, accuracy and linearity prior to use. Deviation from linearity of the semilogarithmic plot of the measured sample activity against time indicates the presence of radiocontaminants.

The most reliable method of checking the linearity of dose calibrators is the decay method (*4*). By using an ultra-pure radionuclide (with no radionuclidic contaminants) and allowing it to decay over a period of several half-lives, while recording its activity at various time intervals, a linear time-activity plot may be achieved. In this case, the obtained linearity is an indication of a linear dose calibrator over the activity range tested, which was from several hundred Megabecquerels to 370 kBq (10 μCi). Commonly, the linearity of dose calibrators in nuclear medicine laboratories is checked with ^{99m}Tc equivalent to that activity which is in the largest patient dose. Activity measurements are taken over an extended period of 3–4 days.

Needless to say, in addition to the lengthy period of activity measurements, deviation from linearity may occur (*5,6*) when the isotope decays down to the level of several hundred of kilobecquerels. This deviation is due to the ^{99}Mo breakthrough that takes place during the ^{99m}Tc elution process of the ^{99}Mo generator. In recent years, several institutions, including ours, have been involved in clinical PET imaging. The use of positron-emitting radiopharmaceuticals is distinctively different from routine gamma emitters due to their 511-keV annihilation photon energy. Although the use of ^{99m}Tc as a test source for linearity measurements has been

suggested (7), the validity of this can be questioned in the current case, where positron emitters are employed. In this investigation, linearity measurements were performed with four commonly used positron emitters, ^{18}F, ^{13}N, ^{11}C and ^{15}O, and deviations from linearity due to possible contaminants were studied.

MATERIALS AND METHODS

Production of Positron Emitters

Fluorine-18. The ^{18}F target system is a water target which is designed for the production of ^{18}F-fluoride. Fluorine-18 is formed by the bombardment of protons on enriched ^{18}O-water by the $^{18}O(p,n)^{18}F$ nuclear reaction (8). To minimize the production of ^{13}N ($T_{1/2}$ = 10 min) via the $^{16}O(p,\alpha)^{13}N$ nuclear reaction, an isotopic purity of ^{18}O greater than 95% is essential. Although the half-lives of ^{13}N (10 min) and ^{18}F (110 min) are considerably different, the isotopic purity of ^{18}O-water should be taken into consideration from the very start. Since high isotopic purity of ^{18}O-water is generally quite costly, the target volume is kept to a minimum (<1 ml), thereby requiring less expense for water. Routinely, we produce 18.5 GBq (500 mCi) of ^{18}F in a 30-min bombardment at 20 μA. A shorter-lived isotope of either oxygen or fluorine is presumably produced by the following reactions but very soon decays down during the radiochemical synthesis (9):

$$^{14}N(p,n)^{14}O \qquad ^{18}O(p,2n)^{17}F,$$

where the half-lives of ^{14}O and ^{17}F are $T_{1/2}$ = 70.91 sec and $T_{1/2}$ = 66.6 sec, respectively.

Nitrogen-13. Nitrogen-13 is a cyclotron-produced radionuclide with a half-life of 10 min, which decays (100%) by the emission of positrons having a maximum energy of 1.19 MeV to the stable nuclide ^{13}C. It is produced by the bombardment of water of natural oxygen isotopic abundance via the $^{16}O(p,\alpha)^{13}N$ nuclear reaction using the 17.5-MeV Scanditronix MC17F Cyclotron. The target chamber contains about 5 ml of target water and can withstand up to 50 μA of the beam current. Typically, a 15-min bombardment of 10 μA produces 18.5 MBq (500 μCi) of ^{13}N as either nitrate or nitrite. As in the case of ^{18}F, a considerable contamination of ^{18}F produced via the $^{18}O(p,n)^{18}F$ nuclear reaction is possible in this reaction. As opposed to the ^{18}F situation where ^{13}N decays because of its much shorter half-life, the ^{18}F contamination may be of significant importance in ^{13}N samples while determining the linearity.

Carbon-11. Carbon-11 is a cyclotron-produced radionuclide having a half-life of 20.3 min and decays (99.8%) by positron emission having a maximum energy of 0.98 MeV to the stable nuclide ^{11}B. It is produced by the bombardment of ultra-high purity N_2 gas of natural isotopic abundance containing 0.01% added oxygen via the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using the 17.5 MeV of the Scanditronix MC17F Cyclotron. Following bombardment of a bolus of target gas, it is released through a trap containing CuO at about 750°C to ensure quantitative conversion of ^{11}C to $^{11}CO_2$. The $^{11}CO_2$ is then removed from the gas stream and concentrated in a trap cooled by liquid nitrogen and brought into the hot cell using a steady flow of N_2 gas and bubbled through a 1-*M* NaOH solution thereby converting it to $NaH^{11}CO_3$.

Oxygen-15. Oxygen-15 is a cyclotron-produced radionuclide with a half-life of 2.07 min that decays (100%) by the emission of positrons having a maximum energy of 1.7 MeV to the stable nuclide ^{15}N. It is produced by the deuteron bombardment of high-purity nitrogen gas containing 1% added oxygen to serve as carrier via the $^{14}N(d,n)^{15}O$ nuclear reaction. As in the case of ^{11}C, ^{15}O is converted to $C^{15}O_2$ which is converted to $NaHC^{15}O_3$ by bubbling through a 1-*M* NaOH solution in the hot cell.

Radioisotope Contaminants Considerations

As mentioned previously, the percentage of radioisotope contaminants depends on the purity of the bombarded target. In the case of ^{18}F studies, the measured activity of the isotope contains the activity of the contaminant ^{13}N which was produced due to the target impurity. Long-lived contaminants will show deviation from linearity, as in the case of ^{13}N contaminated with ^{18}F. Hence, the measured activity (A_t) at any time (t) is the sum of both activities F_t and N_t of the isotopes ^{18}F and ^{13}N, respectively.

Therefore,

$$A_t = F_0e^{-\lambda_F t} + N_0e^{-\lambda_N t}, \qquad \text{Eq. 1}$$

where F_0 is the activity of ^{18}F at time t = 0; N_0 is the activity of ^{13}N at time t = 0; λ_F is the decay constant of ^{18}F; and λ_N is the decay constant of ^{13}N.

On a routine basis, when the purity of the bombarded target is known, an estimate of the contaminant fraction f_0 within the total activity produced during this process may be obtained. At time of production of ^{18}F, the fraction of the contaminant ^{13}N is expressed as:

$$f_0(N) = N_0A_0^{-1}, \qquad \text{Eq. 2}$$

where the fraction at any time (t) is:

$$f_t(N) = N_tA_t^{-1}. \qquad \text{Eq. 3}$$

The inverse of Equation 3 with some manipulation, yields the following expression:

$$\frac{1}{f_t(N)} = 1 + \left(\frac{1 - f_0(N)}{f_0(N)}\right)e^{-(\lambda_F - \lambda_N)t}. \qquad \text{Eq. 4}$$

Similarly, the expression for the contaminant ^{18}F at any time (t) following the production of ^{13}N is:

$$\frac{1}{f_t(F)} = 1 + \left(\frac{1 - f_0(F)}{f_0(F)}\right)e^{-(\lambda_N - \lambda_F)t}. \qquad \text{Eq. 5}$$

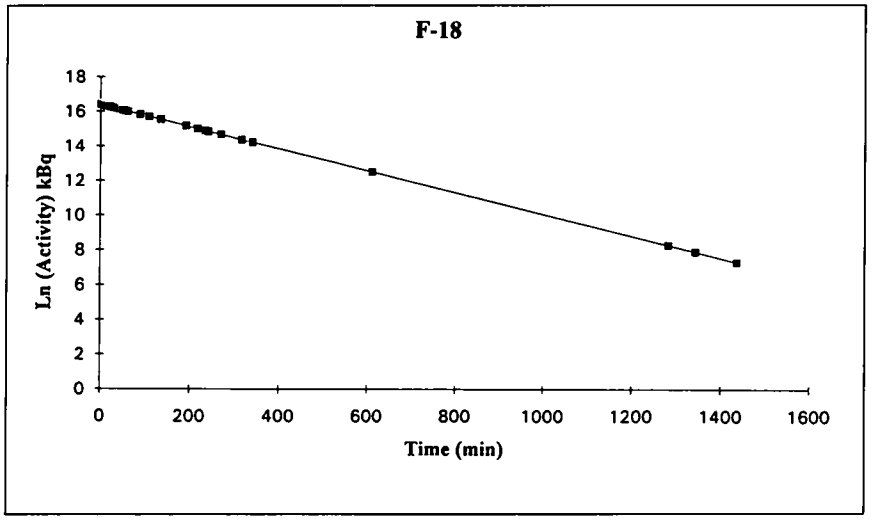

FIGURE 1. Semilogarithmic plot of ^{18}F activity against elapsed time (min). $T_{1/2}$ = 110 min; initial activity of sample = 13.838 GBq (3.74 × 10^5 μCi).

From the above equations, it can be shown that for a contamination level of 5% of ^{13}N at production time, it then diminishes to 0.12% 60 min later, while the same percentage of ^{18}F contamination grows to 25.8% 30 min later and reaches just below the 70% level an hour after production. Hence, it is obvious that the contaminant ^{18}F is critical in the production of ^{13}N and should be minimized, while a small percentage of ^{13}N contamination in the ^{18}F product virtually has no effect on linearity studies 1-hr postproduction of the isotope.

Determination of Linearity

Using the decay method, the linearity was checked in a dose calibrator (RADCAL Model 4050) which was previously calibrated to measure all four positron emitters discussed in the current manuscript. The dose calibrator was also checked for constancy, accuracy and geometry on a routine basis (*10*). About 19.6 GBq (530 mCi) of ^{13}N, 13.8 GBq (374 mCi) of ^{18}F samples, 2.3 GBq (63 mCi) of ^{11}C samples and 2.29 GBq (62 mCi) of ^{15}O samples were studied for this purpose. Each sample was collected in a 10-ml Wheaton vial and placed in the ionization chamber of the dose calibrator located inside the hot cell which was closed for the entire linearity testing period. All the manipulations inside the hot cell were performed with the aid of a mechanical arm (Master Slave Manipulator) which was externally operated. For convenience and easy recording, the display unit was placed outside the hot cell. Several activity measurements at various times were taken until the activity decayed down to the 370-kBq (10 μCi) level for each isotope. Appropriate time-activity curves in semi-logarithmic plots were generated as shown in Figures 1 through 4.

RESULTS AND DISCUSSION

The purity of the four positron emitters investigated in this study was evaluated using the dose calibrator. Time-activity curves of ^{18}F, ^{13}N, ^{11}C and ^{15}O samples were generated (Figs. 1–4). All ^{18}F, ^{11}C and ^{15}O samples showed a virtually linear relationship throughout the activity range tested. However, the ^{13}N samples showed significant deviation from linear response even at the MBq levels due to the presence

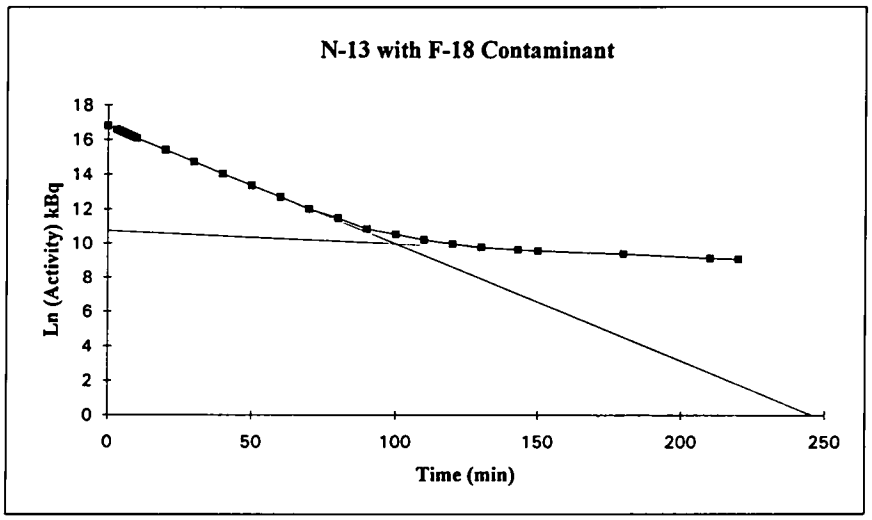

FIGURE 2. Semilogarithmic plot of ^{13}N activity against elapsed time (min). $T_{1/2}$ = 10 min; initial activity of sample = 19.61 GBq (5.30 × 10^5 μCi); ^{18}F contaminant activity (extrapolated) = 27 MBq (730 μCi). The activities of ^{13}N and ^{18}F are equal at the intersection point of the extrapolated lines (at 105 min).

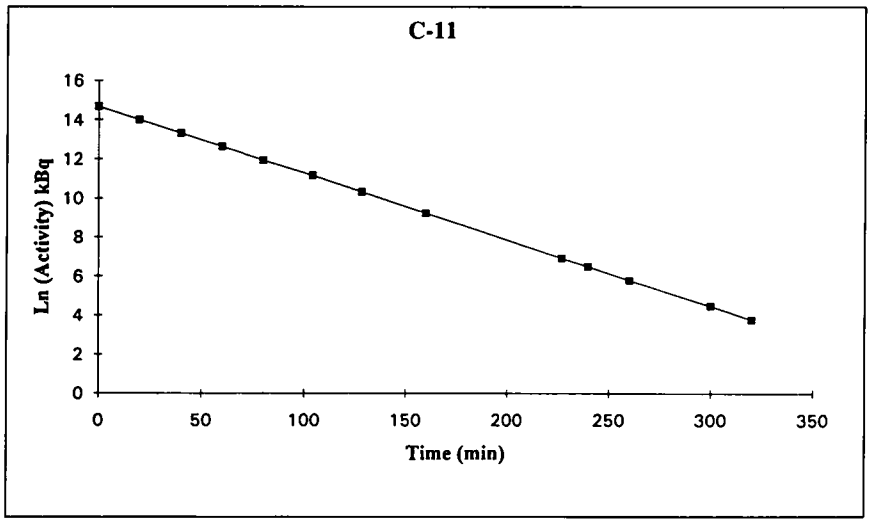

FIGURE 3. Semilogarithmic plot of ^{11}C activity against elapsed time (min). $T_{1/2}$ = 20.3 min; initial activity of sample = 2.346 GBq (6.34×10^4 μCi).

of the contaminant isotope ^{18}F ($T_{1/2}$ = 110 min). This contaminant occurs due to the natural abundance of ^{18}O in water (*11*) and is created during the proton bombardment of the water target in the cyclotron during the production process of ^{13}N via the nuclear reaction $^{18}O(p,n)^{18}F$.

The plot in Figure 2 shows a clear deviation from linearity at 75-min postproduction of the isotope. The plot is extremely linear from the time of production (t = 0) up to this point where significant decay of ^{13}N already occurred. Linear extrapolation of this part of the curve, until it intersects with the time axis, represents the decay of ^{13}N without the presence of the contaminant ^{18}F. Similarly, an extrapolation of the lower part of the curve yields the decay of the contaminant alone, where the activity at production time (t = 0) may be evaluated from its intersection with the natural logarithm (activity) axis. The intersection of the extrapolation lines with each other is the time when the activities of ^{18}F and ^{13}N are equal. In the current study, this point occurs around 105 min postproduction and the activity of each isotope is approximately 13.3 MBq (360 μCi) where, at time of production, the estimated activity of the contaminant was 27 MBq (730 μCi). Hence, in this case, the study shows high purity of ^{13}N at time of production (better than 99.8%) which then deteriorated 105 min later to 50%.

Due to the rapid decay of this isotope and the accelerated deterioration of purity, it is imperative that linearity studies using ^{13}N samples be performed as soon as possible (30–60 min) following the production of the isotope. In the case of the ^{18}F activity plot (Fig. 1), no deviation from linearity in the first part of the curve is recognized due to the low level of the ^{13}N contaminant in the sample. A contamination level of a small percentage at the time of production will be reduced to a negligible level within the two-half-life period of the contaminant ^{13}N. It is noteworthy that in a few samples of ^{15}O, the semilogarithmic plot showed some convex characteristics suggesting some sort of breakdown of the chemical compound itself. Since the synthesis of PET radiopharmaceuticals is constantly monitored by a dose calibrator, an argument can be made that using the positron emitters as the test sources for the linearity measurement of dose calibrators being used in PET facilities is appropriate. Due to the short half-lives of positron emitters, linearity can easily be

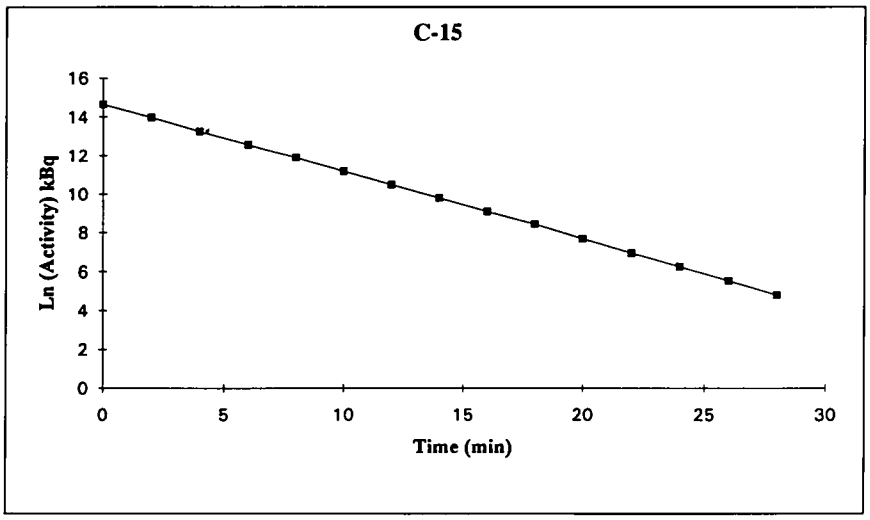

FIGURE 4. Semilogarithmic plot of ^{15}O activity against elapsed time (min). $T_{1/2}$ = 2.07 min; initial activity = 2.297 GBq (6.21×10^4 μCi).

followed over the whole range of the dose calibrator. Although the 2-min half-life of ^{15}O might allow the performance of linearity measurements within minutes, we feel that ^{11}C (Fig. 3) might be an ideal positron emitter to accomplish this task due to its purity and more practical half-life period (20 min).

CONCLUSIONS

Deviation from linearity of decay for ^{18}F, ^{13}N, ^{11}C and ^{15}O was studied using radionuclide dose calibrators. The nonlinear response of the ^{13}N sample was observed even at the MBq level due to significant ^{18}F contamination. Carbon-11 may be an ideal radionuclide for linearity determination of dose calibrators due to its high purity and reasonably short half-life (20 min). As opposed to conventional decay methods where the user encounters multiple exposure during the handling of a high-activity ^{99m}Tc source, the radiation exposure of positron emitters was negligible since the entire study was conducted in a shielded fume hood. In summary, for institutions involved in PET, the use of positron emitters can be an alternative for performing the linearity testing of dose calibrators since the isotopes are available in high purity and the entire determination can be completed in a short time.

ACKNOWLEDGMENTS

Part of this manuscript was presented at the International Symposium on Emerging Frontiers in Radiation Biology (under the auspices of the Indian Society for Radiation Biology and the Indian Society for Radiation and Photochemical Sciences), Bhabha Atomic Research Center, Bombay, India, December 1–3, 1993.

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