Annals of Nuclear Medicine Vol. 8, No. 4, 239–243, 1994

Optimal dose of injection in activation study with O-15 water and PET

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In activation studies with the bolus method for O-15 water and PET, the radiotracer concentration may reach the limits of the system in terms of dead time correction and accidental coincidence. To obtain the optimal injection dose of O-15 water, we performed a normal volunteer study to evaluate the relationship between the injected dose and the radioactivity concentration in the brain and a phantom study to evaluate the performance of the PET scanner (PCT3600W) under high count rate conditions and the effect of averaging on the signal to noise ratio for the PET images.

A linear relationship was noted between the injected dose (normalized for each body weight: x) and the mean radiotracer concentration in the brain measured by PET (y) ($y = 2.52 + 30.1\,x$, $n = 64$, $r = 0.87$, $p < 0.001$). The percent error in the measurement of radioactivity with PET was within $\pm 5\%$ in the 100 to 2000 nCi/m*l* (3.7–74 KBq/m*l*) range. Below 100 nCi/m*l* (3.7 KBq/m*l*), the percent error increased due to the rapid increase in noise in the reconstructed images. Over 1000 nCi/m*l* (37 KBq/m*l*), on the other hand, the noise was almost unchanged.

With our PET scanner, the optimal range of the radiotracer concentration in the brain is below 1000 nCi/m*l* (37 KBq/m*l*), corresponding to an injection dose of 33 mCi (1.22 GBq)/60 kg body weight. With the same total dose, the increment of number of repeated measurements for averaging provided the better signal to noise ratio. In designing a paradigm for an activation PET study, the injection dose and the number of repeated measurements for averaging should be considered.

Key words: PET activation study, O-15 water, optimum dose, signal to noise ratio

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) measurements of regional cerebral blood flow (rCBF) with intravenously administered O-15 labeled water are well suited to the study of the functional-anatomical correlation within the human brain.[1–3] The expression of regional neuronal activation depends on the estimation of the change in rCBF from an initial, basal state. Intra-subject averaging in each state (task loaded, and basal state) is a conventional method used in obtaining a higher signal to noise ratio (S/N ratio) for each state. To obtain greater sensitivity to detect neuronal activity, the S/N of each scanned image should first be enhanced, but under the high count rate conditions encountered in the bolus injection of the O-15 water, it is difficult to know how many more counts are needed to make a noticeable difference in image quality due to dead time loss and increased accidental coincidence.[4] Additionally, intra-subject averaging has limitation in number of repeated measurements, while it is always true that more averaging provides the better S/N ratio.

The purpose of this article is to determine the optimal range of the injection dose and the number of repeated measurements for intra-subject averaging. In order to evaluate the optimal injection dose in terms of the S/N ratio of the images, we performed a normal volunteer study to evaluate the relationship between the injected dose and the radioactivity concentration in the brain and a phantom study to evaluate the performance of the PET

Received February 4, 1994, revision accepted July 1, 1994.

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scanner under high count rate conditions and the effect of image averaging on the S/N ratio of the images.

MATERIALS AND METHODS

Tomograph characteristics

The PCT-3600W scanner (Hitachi Medical Co., Japan) was employed in this study for scanning.[5,6] This scanner simultaneously acquires 15 slices with a center-to-center distance of 7 mm. All scans were performed in a stationary scan mode at a resolution of 9 mm full width at half maximum (FWHM) in transaxial direction and 6.5 mm in the axial direction. The field of view and the pixel size of the reconstructed images were 256 mm and 2 mm, respectively. Prior to all emission measurements, tomographic transmission data were obtained with a Ge-68/Ga-68 standard plate source for the calculation of regional attenuation coefficients. This scanner was cross calibrated with a cylindrical phantom with a diameter of 20 cm and F-18 solution.[7]

Human PET study

Subject preparation The data obtained in eight normal volunteers between the ages of 20 and 25 who were involved in the finger movement paradigm were used in this study.[8] The study was approved by the Ethical committee of Kyoto University Faculty of Medicine, and informed written consent was obtained from each subject.

Prior to the examination, catheters were placed in the cubital vein and the brachial artery in opposite arms. During scanning, the subjects' heads were immobilized within individually molded head-holders. The subjects' eyes were closed and the room lights were dimmed. Thinking was not restricted.

Tracer techniques We performed 90 second scan acquisition starting at injection of the tracer. Fifteen second dynamic scans of 6 consecutive frames were obtained, and the sinograms were added to make one stationary image.

O-15 labeled water (in total 6 m*l* saline solution) was injected via the right cubital vein in 15 seconds with an automatic injector.[9] The volume and activity of the residual radiotracer in the syringe were measured and corrected for decay to obtain the injected dose. The injected activity ranged from 11 to 39 mCi (410 to 1440 MBq). In each subject, eight PET measurements were performed at 10 to 15 min intervals with various task states including the basal control condition.

Reconstruction of the images PET images were reconstructed by means of a standard filtered back-projection algorithm on to a 128 × 128 matrix of 2 mm pixel size. Data were corrected for dead-time based on the singles rate per crystal block. Random coincidence correction was performed with the observed detector singles rate and the coincidence window to calculate the random rate ($S_1S_2 \times 2$ t method).[10] Attenuation correction was performed by using the matched transmission scan data.

Relationship between injected dose and cerebral radiotracer concentration The global cerebral radiotracer concentration was determined for each scan by averaging the tissue radiotracer concentrations from all pixels which are 30% or more the maximal values for the all pixels in the 15 slices data.[9]

Phantom study

Quantitation under low count rate The 20 cm diameter cylinder, which we use for cross calibration of the scanner and well counter,[7,9] contained F-18 solution with a concentration of 1800 nCi/m*l* (67 KBq/m*l*). The concentration of F-18 solution was measured by the well counter after sufficient decay, and the radioactivity in the phantom at each frame (standard value) was obtained with the value measured by the well counter and known decay time. Twenty frames for every one minute dynamic scan were obtained. These data were reconstructed and calibrated according to the same conditions as in the clinical study. The same procedure was repeated on additional 4 times with different concentrations in the phantom, which were actually obtained by waiting for the decay of the F-18 solution mentioned above. The average and standard deviation in the region of interest (ROI), which included the central 80% of the cylinder, was measured.

Percent error (% error) was calculated by means of the following equation:

$$\%\ \text{error} = \frac{(\text{mean value in ROI}) - (\text{standard value})}{\text{standard value}} \times 100.$$

Quantitation under high count rate The 20 cm diameter cylinder was filled with O-15 water at a concentration of 4000 nCi/m*l* (150 KBq/m*l*). A twenty frame per 20 min dynamic scan was performed. The data were reconstructed and calibrated according to the same conditions as in the clinical study. No decay correction was performed. In this O-15 water study, sampling was not performed because of the short half life of O-15 water. Instead, the mean value for a ROI at the frame taken under a low count rate (270 nCi/m*l*, 10 KBq/m*l*) was used as the standard value, and the radioactivity concentrations of other frames were calculated with this standard value and the known half life of O-15.

With the mean and standard deviation (SD) in the same ROI as mentioned above, the % error and coefficient of variation (COV) were calculated.

Effect of Averaging To evaluate the effect of averaging, the data obtained for the previous evaluation of quantitation under the low count rate with a 20 cm diameter cylinder filled with F-18 solution were used. The initial ten frames of every one minute dynamic PET scan in each measurement were used for the calculation of the signal to noise (S/N) ratio for the PET images. Radioactive decay was corrected to the starting time for each scan, generating 10 images of the same radiotracer concentra-

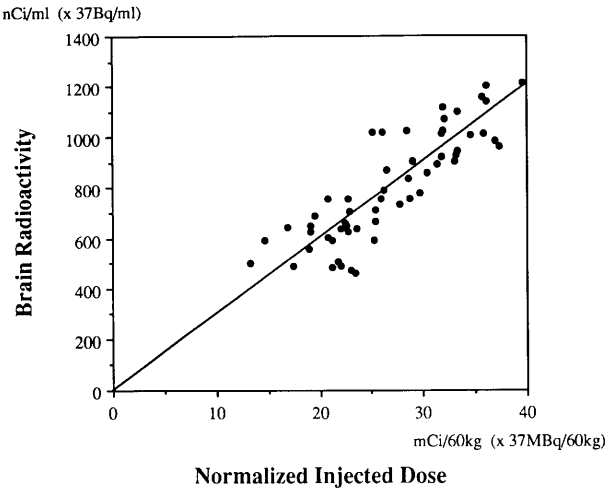

Fig. 1 Global brain concentration of the radioactivity (y) and the injected dose of O-15 water which was normalized to 60 kg body weight (x). A linear relationship is noted ($y = 2.52 + 30.1\ x$, n = 64, r = 0.87, $p < 0.001$).

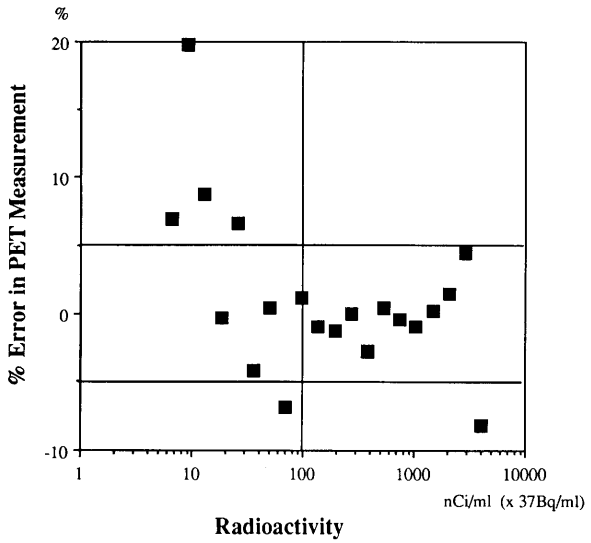

Fig. 2 Performance of PET scanner at high and low count rates. Percent error (% error) of radioactivity within ROI in the cylinder phantom filled with O-15 water measured by PET was plotted against true radioactivity (semilogarithmic plot). Note that below 100 nCi/m*l* (3.7 KBq/m*l*) and over 3000 nCi/m*l* (111 KBq/m*l*), % error increases.

tion. With these images, the averaging of 2 to 10 times repeated measurements was performed. After selecting the central slice of the phantom images, the mean value and SD were measured in ROI in each image with a different number of repeated measurements for averaging. S/N (= mean/SD in ROI) was plotted against the number. The same procedure was repeated on additional 4 times with different concentrations in the phantom, which were actually obtained by waiting for the decay of the F-18 solution mentioned above.

RESULTS

Human PET study

Figure 1 shows the relationship between the injected dose (normalized to 60 kg body weight; x) and the global brain radiotracer concentration in 8 subjects measured with a PET scanner (y). The results indicated the linear correlation between the injected dose and the brain activity ($y = 2.52 + 30.1\ x$, n = 64, r = 0.868, $p < 0.001$).

Phantom study

Quantitation under low and high count rates In the 287 to 648 nCi/m*l* (11 to 24 KBq) of radioactivity range, the percent error (% error) of the measurement of radioactivity with PET and F-18 solution was within ± 3% (0.54 ± 0.98%, mean ± SD, n = 60). Figure 2 shows the % error in the wider range of measurement with O-15 water. It was within ± 5% (−0.34 ± 1.26, n = 11) in the range 100 to 2000 nCi/m*l* (3.7 − 74 KBq/m*l*). Below 100 nCi/m*l* (3.7 KBq/m*l*), the % error increased (3.6 ± 8.0%, n = 9) as expected. On the other hand, the % error also tended to be larger in the range over 3000 nCi/m*l* (111 KBq/m*l*). Figure 3 shows the relationship between radioactivity in the phantom and the coefficient of variation

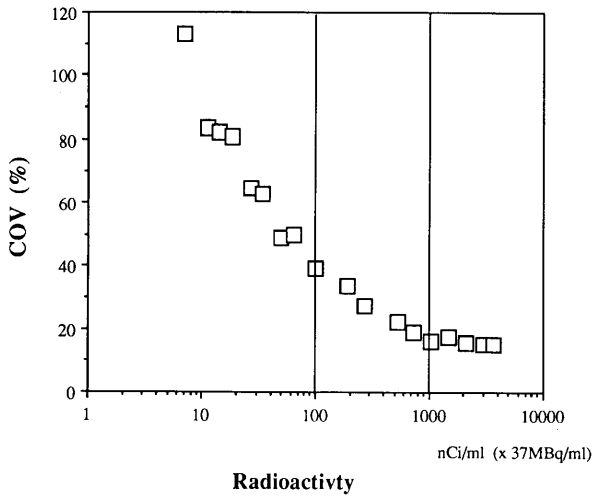

Fig. 3 Noise, expressed as a coefficient of variation (COV) within ROI over a flood phantom image of O-15 water, plotted against the radioactivity (semilogarithmic plot). Note that COV decreases when the radioactivity increases, but over 1000 nCi/m*l* (37 KBq/m*l*), noise is almost unchanged.

(COV) of the reconstructed images. COV which represents noise in the reconstructed PET images increased rapidly below 100 nCi/m*l* (3.7 KBq/m*l*). Over 1000 nCi/m*l* (37 KBq/m*l*), on the other hand, COV was almost unchanged.

Effect of averaging Figure 4 shows the effect of averaging on the S/N ratio of the PET images with different concentrations of F-18 solution in the phantom. We estimated the global radioactive concentration in the brain

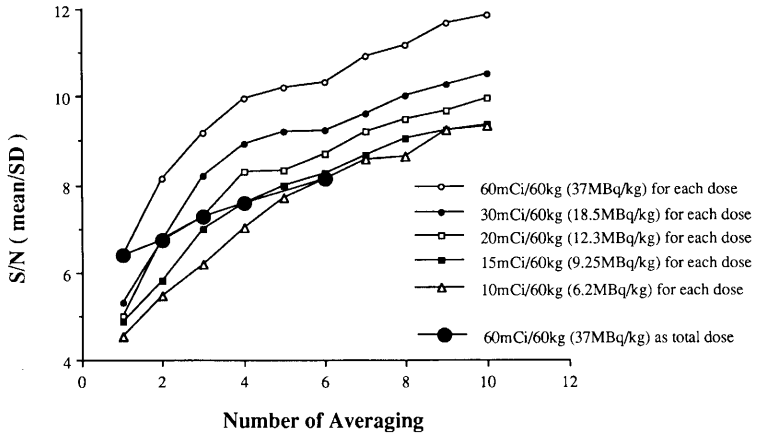

Fig. 4 S/N ratio, expressed as mean/SD within ROI over an averaged phantom image of F-18 solution with different radiotracer concentrations, plotted against the number of averaging in each image. The radioactivity was converted to the injection dose normalized to body weight (60 kg) instead of showing radiotracer concentration in the phantom. The large solid circles represent the values corresponding to the same total dose injected, 60 mCi/60 kg body weight (37 KBq/kg), with different number of averaging.

with O-15 water by using the linear relationship shown in Figure 1. The initial F-18 concentration in the phantom (1800 nCi/m*l*, 67 KBq/m*l*) corresponded to the global brain activity following the injection of 60 mCi (2.22 GBq) of O-15 water into a subject of 60 kg body weight (or 37 MBq/kg). The data demonstrated improved S/N ratio with an increased number of repeated measurements for averaging at all concentrations. As the total dose administered is usually limited in case of the clinical studies due to the limitation of the radiation dose given to the subjects, the effect of averaging on the S/N ratio of the PET images with the same total dose is also shown in Figure 4. As indicated in the large closed circles, with the same total amount of radiotracer injected (60 mCi for 60 kg body weight, or 37 KBq/kg), the greater the number of repeated measurements for averaging, the greater the S/N ratio.

DISCUSSION

The bolus injection method for O-15 water with PET in the activation study is been well established, and its advantages and disadvantages have been discussed.[11] The bolus method with a sharp peak and short scanning duration is sensitive to delay and dispersion, but provides a linear relationship between integrated tissue activity and flow, resulting in less tissue heterogeneity effect. As the total integration of the activity is almost determined in the first 20 sec after reaching the activity in the brain, the calculated CBF is likely to vary with the fluctuation in CBF. Because of the sharp peak of input function, dead time error and accidental coincidence could be a problem, but the optimal dose of O-15 water in the bolus method has seldom been mentioned. This problem is closely related to the performance of the PET machine at a high count rate.

In PET measurements, accidental coincidence increases in proportion to the square of radioactivity in the field of view, but the true coincidence rate is essentially proportional to the radioactivity.[10,12] There is also an increase in the count loss due to the dead time of the detectors. The correction algorithms for accidental coincidence and dead time loss are usually built into commercial PET systems, but the large fraction of accidental coincidence in the high count rate interferes with the increase in the actual signals, and the S/N ratio of the images may decrease due to inappropriate correction. It is therefore important to determine the optimal range of the injection dose required in order to obtain the maximum S/N ratio. As the optimal range of the injection dose is machine dependent as well as protocol dependent, the evaluation shown in this article should be performed at each institute with its own protocol for CBF measurement. Our phantom study was designed to evaluate the efficiency of correction of dead time count loss and accidental coincidence, and the S/N ratio of the images at the high count rate for the reconstructed images to evaluate the overall efficacy of the correction. Since our evaluation uses the reconstructed images, it can easily be performed by PET users without any special knowledge of the correction process, and is able to determine the feasibility of data correction and the reconstruction of images.

In our phantom study, a scanning time of 60 sec was chosen to simulate the activation prptocol. In this setting, the quantitation of our PET system was well maintained in the 100 to 2000 nCi/m*l* (3.7 to 74 KBq/m*l*) range which covers the radioactivity encountered in the usual activation study with the bolus injection. In terms of image noise, however, the radioactivity over 1000 nCi/m*l* (37 KBq/m*l*) rarely contributes to the improvement in the S/N ratio of PET images. This is probably caused by

increased accidental coincidence. This radioactivity concentration of 1000 nCi/ml (37 KBq/ml) in the brain is expected when 30 to 40 mCi (1.1 to 1.5 GBq) of O-15 water is injected into a subject with a body weight of 60 kg. In terms of the S/N ratio of the individual image as well as radiation exposure to the subjects, the dose of O-15 water injected should not exceed 30–40 mCi/60 kg in our protocol.

In this study, we used a cylindrical phantom 20 cm in diameter, which is slightly larger than the *in vivo* human brain. Since the S/N ratio of the reconstructed images is essentially determined by the radioactivity in the field of view, the phantom size should be close to that of the brain for simulation of this kind.

In activation studies, the averaging of images is usually performed to improve the S/N ratio of the images of a state (such as control and task loaded). Since total integration is almost determined in the first 20 sec with the bolus method,[11,12] it is difficult to decrease noise by elongating the scan time. Our study demonstrated that with the same total radioactivity, more averaging provided a better S/N ratio of images.

The number of repeated measurements for averaging in a subject may be limited by other factors such as fatigue or habituation, or total radiation exposure. In the usual activation design, 6 to 8 scans per subject is common, considering the examination time (approximately a 10 to 12 min scanning interval). Under these restrictions, the number of repeated measurements for averaging should be maximized to obtain the least noisy images for each state (control and task loaded). Assuming that a subject weighing 60 kg receives 8 injections of 35 mCi (1.3 GBq) of O-15 water, the total amount of O-15 water would not exceed 300 mCi (11 GBq), and the absorbed dose to the total body of the individual subject would be less than 5 mGy.[13] In this discussion, we are dealing only with intra-subject averaging to avoid complexity due to the anatomical variation encountered in inter-subject averaging.[14]

In conclusion, the injection dose of O-15 water and the averaging number in the activation study should be determined by machine performance at a high count rate. With the O-15 water bolus method and our PCT 3600W system, a single injection dose more than 33 mCi (1.22 GBq)/60 kg body weight would not be advantageous in terms of the S/N ratio, and the number of repeated measurements for averaging should be maximized with the same amount of total radiotracer activity.

ACKNOWLEDGMENTS

This work was supported in part by a Japan Ministry of Health and Welfare research grant for nervous and mental disorders, and a Grant-in-aid for Scientific Research (06404031) from the Japan Ministry of Education, Science and Culture.

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