Estimation of internal absorbed dose of L-[methyl-^{11}C]methionine using whole-body positron emission tomography

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Abstract. L-[Methyl-^{11}C]-methionine (^{11}C-methionine) is proposed as a useful radiotracer for tumour diagnosis. Human biodistribution data of cumulated activities and absorbed doses estimated by the MIRD (medical internal radiation dosimetry) method for ^{11}C-methionine are not available in the literature. In this study we measured the organ activity for ^{11}C-methionine by using whole-body positron emission tomography (PET) and estimated the absorbed doses to 25 organs by the MIRD method. Whole-body dynamic PET scans were performed on five normal volunteers to measure the time course of the organ activity concentration (activity/volume) after intravenous administration of ^{11}C-methionine. Cumulated activities of the ten source organs were calculated from the time-activity curves, obtained from the dynamic PET data. Absorbed dose estimates were performed by the MIRD method for the Caucasian reference man and for the Japanese reference man. The organs which received the highest absorbed doses for the Caucasian reference man were found to be the bladder wall (2.7×10^{-2} mGy/MBq), the pancreas (1.9×10^{-2} mGy/MBq), the liver (1.8×10^{-2} mGy/MBq) and the kidney (1.1×10^{-2} mGy/MBq). The effective doses for the Caucasian reference man and the Japanese reference man were calculated as 5.2×10^{-3} and 5.0×10^{-3} mSv/MBq, respectively.

Key words: L-[Methyl-^{11}C]methionine – Whole-body positron emission tomography – Cumulated activity – Absorbed dose – MIRD method

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Introduction

L-[Methyl-^{11}C]methionine (^{11}C-methionine) is a very useful radiotracer employed in conjunction with positron emission tomography (PET) for the diagnosis of cancer. Currently no internal dosimetry data for ^{11}C-methionine in humans are available in the literature, all the reported data for ^{11}C-methionine having been based on animal experiments [1, 2]. In this study, after intravenous administration of ^{11}C methionine, organ activity measurements were performed with whole-body PET to define tissue concentrations of the injected radioactive tracer. Absorbed doses were estimated by the MIRD method for the Caucasian reference man [3] and the Japanese/Asian reference man [4].

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Materials and methods

Subjects. Five normal volunteers participated in this study (age: 22–40 years, mean 29±9 years). None of them had a prior history of any major medical illness. All volunteers were asked to refrain from eating and drinking for 4 h before the PET study. All subjects gave their written consent and the Ethics Committee for Clinical Research of Tohoku University approved the study protocol.

Whole-body PET scanning protocol. All studies were done with a whole-body PET scanner (SET-2400W, Shimadzu Co. Ltd., Kyoto, Japan) in 2D mode at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan. The scanner provides 63 continuous transaxial slices with a resolution of 3.9 mm full-width at half-maximum in plane and 4.5 mm axially. The axial field of view is 20 cm [5].

After whole-body transmission scans (to correct the attenuation of the emission data), ^{11}C-methionine was injected intravenously and five repeated whole-body dynamic emission scans were performed in each volunteer. The duration of scanning at each bed position was 2 min for the first three whole-body emission scans. For the last two emission scans the duration was increased to 4 min to achieve better data of organ activity. The average injected dose was 558 MBq (from 474 to 592 MBq). Urine was collected after the last emission scan and radioactivity of the urine was measured with a calibrated Curie-meter.

Organ time-activity measurement. The radioactivities in various source organs were obtained from reconstructed PET images by averaging the activities (cps/ml) of regions of interest (ROIs) in each organ, since the radioactivity distribution within an organ can

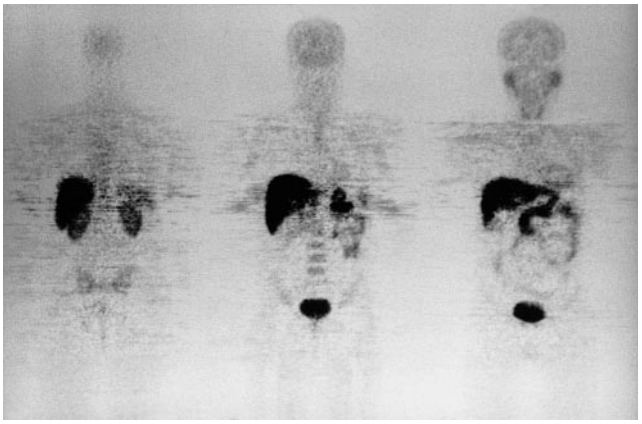

Fig. 1. Coronal whole-body PET images (during the fourth emission scan) with clear visualization of the liver, kidney, pancreas and bladder. Separation between the coronal planes was 3.6 cm

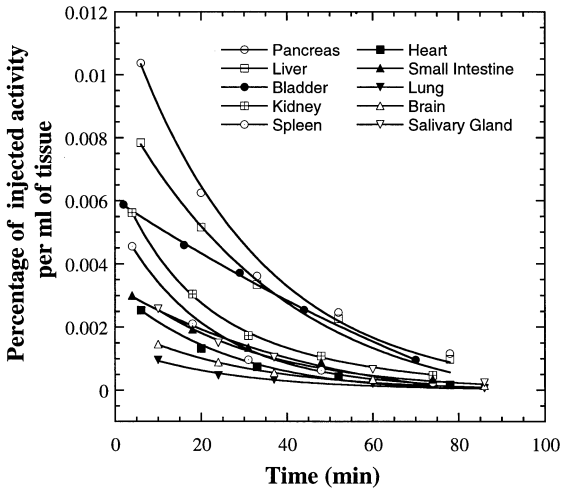

Fig. 2. Typical time-activity curves for the source organs, obtained from the whole-body dynamic emission scans of one volunteer. These curves were fitted with a sum of two exponential functions. As the scanning was started from the bottom of the body, the organs appeared in their bed positions during the scan time

be considered uniform [6]. An example of a whole-body PET image is shown in Fig. 1. ROI analysis was carried out with built-in PET image analysis software. Certain major organs, i.e. the brain, heart, lung, liver, bladder, kidney, spleen, pancreas, small intestine and salivary gland, were considered as the source organs in this study. Polygonal ROIs for these organs were defined according to Herzog et al. [7].

To obtain quantitative radioactivity data for each clinical session, a cross-calibration factor described in the article of Mejia et al. [6] was used. The total bladder activity for the last emission scan was considered as constant until voiding, given the short time interval (7–8 min) between the last emission scan and voiding.

Calculation of cumulated activity. Time-activity curves in ten source organs were obtained from the five repeated whole-body dynamic PET measurements. Typical time-activity curves (example for one volunteer) are shown in Fig. 2. To obtain the cumulated activity of the organ no attempt was made to achieve physical decay correction of the data. All the curves were well fitted with exponential functions including physical decay [6]. The activity remaining in the organ after the last measurement is assumed to decrease only with physical decay [6], since the biological clearance is not known. This gives a conservative estimation of the cumulated activity. Integration of the fitted function from zero to the time of last measurement, plus integration of the function (representing only physical decay) from the time of last measurement to infinity, gave the cumulated activity of the organ [6]. As the times of last emission scan and voiding are different, in order to extrapolate the time-activity curve of the bladder content beyond the scan time, the urine activity (7.4±2.6 kBq/ml) was subtracted from the bladder activity. The organ volumes from the MIRD phantom [3] and the Japanese reference man [4] were considered in order to calculate the organ-cumulated activity and undertake a parallel study for the two reference men [3, 4].

Absorbed dose estimate. The absorbed doses in the 25 target organs were estimated with the MIRD method using the IDES code [8] for the Caucasian reference man and the Japanese reference man. A transformation method was applied to the MIRD S-tables to obtain absorbed doses for the Japanese reference man [6].

The effective dose was calculated according to ICRP 60. In the effective dose calculation an equal tissue-weighting factor was applied to all target organs of the remainder of the body. The skin and the oesophagus were not included in this study, and the weighting factors of these organs were equally allocated to the organ list in the remainder of the body (ICRP 60), which might entail a slight overestimation of the effective dose.

Results

Distribution of the radioactivity per gram of source organ (kBq/g) averaged for the five subjects is shown in Table 1 as a function of time.

The mean cumulated activities per unit activity administered for the two types of organ volume [3, 4] are shown in Table 2, together with the standard deviations. The cumulated activities of the whole body and the remainder of the body were calculated as done by Mejia et al. [6]. The percentage of total uptake of ^{11}C-methionine in the source organs, shown in Table 3, was calculated from the ratio of average cumulated activities of each source organ to the whole body (Table 2).

The mean absorbed doses (with standard deviations) for the Caucasian reference man of 70 kg and the Japanese reference man of 60 kg are shown in Table 4. The target organs that received the highest absorbed doses for the Caucasian reference man were found to be the bladder wall, pancreas, liver and kidney, the doses for these organs being 2.7×10^{-2}, 1.9×10^{-2}, 1.8×10^{-2} and 1.1×10^{-2} mGy/MBq, respectively. For the Japanese reference man the highest absorbed doses were found for the pancreas, liver, bladder and kidney, at 2.7×10^{-2}, 1.7×10^{-2}, 1.5×10^{-2} and 1.2×10^{-2} mGy/MBq, respectively. The mean effective doses for the Caucasian and Japanese reference men were estimated to be 5.2×10^{-3} and 5.0×10^{-3} mSv/MBq, respectively.

Table 1. Activity concentrations (kBq/g[a]) in the source organs, measured by whole-body PET at various times after intravenous injection of ^{11}C-methionine

Organ	Time				
	~2 to ~10 min	~15 to ~23 min	~28 to ~36 min	~43 to ~59 min	~68 to ~84 min
Bladder	30.3±10	69.1±54	55 ±41	31 ±21	17 ±9.4
Small intestine	18.7±5.5	12.7±2.6	8.1±2.9	4.9±1.3	2.3±0.5
Kidney	42.3±11	19.3±3.8	10.9±2.3	6.1±1.1	2.6±0.2
Liver	47 ±4	34.0±4.3	22.6±3	14 ±1.5	6.1±0.5
Lung	1.7±1.1	0.8±0.8	0.5±0.4	0.3±0.4	0.1±0.2
Pancreas	62.5±7	42 ±10	26.5±7.8	16.5±3.2	7.8±1.2
Spleen	24 ±3.7	13.7±3.2	6.9±1.1	4.9±1.9	1.9±0.4
Salivary gland	16.3±1.7	9.7±1.0	6.2±0.9	3.7±0.6	1.5±0.2
Brain	7.1±1.2	4.5±0.7	2.8±0.4	1.7±0.3	0.7±0.2
Heart	17 ±2.2	8.1±0.8	4.5±0.4	2.5±0.3	0.9±0.1

Values are means±SD for the five normal volunteers
[a] The density of organs in the MIRD phantom [3] were used to convert from ml to g

Table 2. Cumulated activity of the source organs per unit administered activity (kBq-h/MBq) of the Caucasian and Japanese reference men [3, 4]

Source organ	Caucasian reference man [3]	Japanese reference man [4]
Bladder	19.1±4.7	4.4±1.1
Small intestine	12.3±3	5.4±3.6
Kidney	10.3±1.4	11 ±1.5
Liver	101 ±7.8	85.3±6.6
Lung	24 ±9.7	26.3±10.6
Pancreas	6.3±0.9	8.7±1.3
Spleen	4.3±0.7	3.3±0.5
Salvary gland	1.8±0.4	1.6±0.4
Brain	13.3±3.2	13.0±3.2
Heart	7.2±0.3	6.3±0.3
Remainder of the body	288 ±24	316 ±22

Values are means±SD

Table 3. Percentage of total uptake[a] of ^{11}C-methionine in the source organs for the Caucasian and Japanese reference men [3, 4]

Source organ	Caucasian reference man [3]	Japanese reference man [4]
Bladder	2.5±0.5	1.1±0.8
Small intestine	4 ±1	0.9±0.2
Kidney	2.1±0.3	2.3±0.3
Liver	20.7±1.6	17.7±1.4
Lung	5 ±2	5.5±2.2
Pancreas	1.3±0.2	1.8±0.3
Spleen	0.9±0.2	0.7±0.1
Salivary gland	0.4±0.1	0.3±0.1
Brain	2.8±0.7	2.7±0.7
Heart	1.5±0.1	1.3±0.1
Remainder of the body	59.1±5.3	65.7±4.6

Values are means±SD
[a] Calculated from their cumulated activities

Discussion

Ten organs in this study were considered as the source organs after visual inspection of the PET images. All the source organs except the lung showed high uptake (see Fig. 2). The highest and lowest percentages of injected activity per ml of organ tissue, namely 0.0131%± 0.0018% (mean ±SD) and 0.0013%±0.003%, were observed in the pancreas and lung, respectively (the pancreas to lung ratio was 10.1), at the time of the first emission scan. The small standard deviations of organ activity concentrations shown in Table 1 demonstrate the consistency among the individual results, except in the case of the bladder. The bladder radioactivity showed large variations at the time of the second, third and fourth emission scans. In the study of Comar et al. [2], human brain uptake measured by a gamma camera was ~0.4% of the injected dose (740 MBq) at 10 min, which translates as 0.08 mCi or 2.96 MBq for the whole brain and 0.004 MBq per unit administered activity (1 MBq). By contrast in our study the average activity (from Table 1) for the whole brain for 1370 ml [3] was 9.35 MBq and 0.0166 MBq per unit administered activity, i.e. about 4.15 times higher than the results of Comar et al. [2].

In the calculation of cumulated activity, only physical decay after the last measurement was assumed, which may have caused overestimation of cumulated activities as well as absorbed doses. As the mean results of cumulated activities in Table 2 were calculated from each individual, standard deviations are shown with these results. The variations in the cumulated activities of the source organs shown in Table 2 for the two different reference men [3, 4] arose due to the difference in organ volumes.

In this study the MIRD model gave a relatively high absorbed dose to the bladder wall, and it is to be noted that the absorbed dose to the bladder wall calculated with the MIRD model is higher than that obtained with

Table 4. Estimated absorbed doses of ^{11}C-methionine (mGy/MBq) for the target organs in this study, compared with results obtained by Stalnacke

Target organ	Caucasian reference man [3][a]	Japanese reference man [4][a]	Stalnacke [1]
Testes	2.2E-03±1.4E-04	2.6E-03±1.6E-04	
Red marrow	8.3E-04±2.3E-05	8.5E-04±2.5E-05	
ULI (wall)	3.3E-03±1.4E-04	3.2E-03±1.0E-04	
LLI (wall)	2.5E-03±1.3E-04	2.8E-03±1.5E-04	
Lung	7.4E-03±2.1E-03	8.5E-03±2.4E-03	
Stomach (wall)	2.9E-03±6.8E-05	3.4E-03±6.0E-05	
Bladder (wall)	2.7E-02±4.8E-03	1.5E-02±8.8E-03	
Breast	2.0E-03±4.8E-05	2.5E-03±4.7E-05	
Liver	1.8E-02±1.1E-03	1.7E-02±1.1E-03	1.2E-02
Thyroid	2.1E-03±1.1E-04	2.6E-03±1.1E-04	
Bone surface	1.1E-03±1.4E-05	1.3E-03±1.9E-05	
Adrenal	3.7E-03±4.3E-05	4.2E-03±2.5E-05	
Brain	3.4E-03±6.2E-04	3.8E-03±7.0E-04	
Small intestine	4.5E-03±5.3E-04	3.0E-03±1.5E-04	2.4E-02
Kidney	1.1E-02±1.1E-03	1.2E-02±1.2E-03	2.7E-02
Pancreas	1.9E-02±2.0E-03	2.7E-02±3.2E-03	3.5E-02
Spleen	7.9E-03±8.4E-04	7.4E-03±7.6E-04	
Thymus	2.4E-03±5.7E-05	2.8E-03±5.9E-05	
Heart wall	7.6E-03±2.9E-04	7.9E-03±3.1E-04	
Major airway (wall)[b]	2.9E-03±1.2E-04	3.6E-03±1.2E-04	
Nasal cavity (wall)[b]	5.4E-03±5.0E-04	5.8E-03±6.8E-04	
Ribs	2.4E-03±3.7E-05	2.9E-03±3.3E-05	
Skull	1.8E-03±7.9E-05	2.2E-03±9.8E-05	
Spine	2.8E-03±6.8E-05	3.3E-03±6.3E-05	
Pelvis	2.4E-03±1.2E-04	2.7E-03±1.5E-04	
ED (mSv/MBq)	5.2E-03±4.5E-04	5.0E-03±5.1E-04	

Values are means±SD
(ULI, Upper large intestine; LLI, lower large intestine; ED, effective dose
[a] Present study
[b] S-values were used from ref. [10] and the cumulated activity of the salivary gland was used to calculate the absorbed dose of the nasal cavity wall

the dynamic bladder model [9]. The absorbed doses to the small intestine, kidney, liver and pancreas have been compared in Table 4 with the results reported by Stalnacke [1], which were calculated from data obtained in the mouse and pig and, in the case of the kidney, from the use of selenium-75 methionine in humans. Some differences can be seen between our estimated doses and Stalnacke's results [1].

In conclusion, in this study the critical organs for the Caucasian reference man were found to be (in descending order) the bladder wall, the pancreas and the liver, while for the Japanese reference man they were the pancreas, the liver and the bladder wall. These are the first experimental human dosimetry data available for ^{11}C-methionine, and they provide valuable information on the risk posed by various injected doses of ^{11}C-methionine.

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