PHYSICS AND RADIATION BIOLOGY

The Radiation Dosimetry of 2-[F-18]Fluoro-2-Deoxy-D-Glucose in Man

Stephen C. Jones, Abass Alavi, David Christman, Irving Montanez, Alfred P. Wolf, and Martin Reivich

University of Pennsylvania, Philadelphia, Pennsylvania and Brookhaven National Laboratory, Upton, New York

Bladder and brain time-activity measurements in humans were performed after the intravenous administration of 2-[F-18]fluoro-2-deoxy-D-glucose. Radiation doses were calculated using the MIRD schema. The bladder wall received an average of 440 mrad/mCi (s.e. 76) in ten subjects who voided at 2 hr after administration of tracer. If these subjects had voided at 1 hr, the bladder-wall dose would have been reduced to 220 mrad/mCi. The brain received an average of 81 mrad/mCi in eight subjects. The doses to other organs, calculated from published dog biodistribution data, are between 50 and 85 mrad/mCi except for spleen and heart, which both received 160 mrad/mCi. These time-activity measurements for the critical organ in the human avoid the assumptions made in using animal biodistribution data for human dosimetry calculations.

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2-Fluoro-2-deoxy-D-glucose (2FDG), labeled with fluorine-18 ($T_{1/2}$ = 109 min), is used in conjunction with positron emission tomography (PET) by several laboratories for the measurement of the cerebral metabolic rate of glucose, a technique developed by Reivich et al. (*1*,*2*) and subsequently modified by Phelps et al. (*3*). 2FDG(F-18) is a glucose analog that is transported across the blood-brain barrier and phosphorylated, but is not metabolized further. The organ that receives the highest radiation dose from the use of this compound is the bladder wall. Urinary excretion of 2FDG(F-18) occurs because the compound passes through the glomerulus but is not completely reabsorbed by the tubule (*4*). Up to this time, animal biodistribution data (*5*) have been used to evaluate the radiation dose to the human bladder wall (*2*,*6*). Human data would, of course, be preferable. Consequently we have undertaken bladder time-activity measurements in human subjects who were undergoing measurements of brain metabolism with 2FDG(F-18). In addition, the radiation dose to the brain was calculated from brain uptake in these same subjects. As part of this work, the radiation dose to the other organs was calculated using the dog biodistribution data of Gallagher et al. (*5*).

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For reprints contact: Stephen C. Jones, PhD, Cerebrovascular Research Center, Rm. 429 Johnson Pavilion, 36th and Hamilton Walk, University of Pennsylvania, Philadelphia, PA 19104.

METHODS AND MATERIALS

Human subjects. The eleven subjects studied ranged in age from 20 to 68 yr. Informed consent was obtained for the measurement of the cerebral metabolic rate of glucose. The bladder time-activity measurement did not interfere with this procedure.

Activity measurements. The amount of activity injected was assayed in a calibrated ion chamber. The activity of urine and 2FDG(F-18) aliquots were assayed with a Na(Tl) well counter and scaler.

Bladder time-activity measurements. Fluorine-18 activity in the bladder was monitored with a heavily collimated sodium iodide probe in ten subjects for 2 hr after intravenous 2FDG(F-18) administration. The time courses were obtained on a strip-chart recorder and gave the relative activity in the bladder. The activity in overlying and underlying tissue was not substantial, as we confirmed by making measurements of activity adjacent to the bladder with the collimated probe, so that this single-probe analysis of the time course was considered sufficient. To ensure that the subjects had empty blad-

ders at the beginning of the study and full bladders after 2 hr, they drank two glasses of water 1 hr before the study, voided immediately before injection, and drank two more glasses of water. Two hours after injection, subjects voided again. The amount of activity in the bladder, A_{BC}, was assessed from total voided urine volume and by measurement of the activity in a urine aliquot. The percent of injected activity in the bladder was calculated by decay-correcting the activity A_{BC} to injection time and dividing by the injected activity. To check whether the subjects had completely emptied their bladders, the activity over the bladder was determined before and after the 2-hr void in four subjects. In all ten subjects the amount remaining in the bladder after the background had been subtracted was always less than 7%. Two subjects drank two glasses of water at 2 hr after injection and voided at 4 hr, so that the percent of injected activity accumulated in the bladder between 2 and 4 hr could be determined.

Calculation of cumulated activity for the bladder contents. The cumulated activity for the bladder contents, $\tilde{A}_{BC}$ (μCi-hr), and the area under the time-activity curve, R (cpm-hr), are related to the amount of injected dose in the bladder at 2 hr, A_{BC} (μCi), and the height of the time-activity curve at 2 hr, H (cpm), by the proportionality

$$\frac{\tilde{A}_{BC}}{A_{BC}} = \frac{R}{H}. \quad (1)$$

Thus the cumulated activity $\tilde{A}_{BC}$ can be calculated for each of the ten subjects from the measured quantities R, A_{BC}, and H. R and H were evaluated from the bladder time-activity curve (Simpson's rule was used to calculate the area R). The efficiency of the NaI probe cancels in the above proportionality. A_{BC} was determined, as described above, by counting an aliquot of the 2-hr void.

Brain uptake of F-18. The brain uptake of F-18 from 2FDG(F-18) was determined in eight subjects. The average F-18 concentration (μCi/g) was determined from a PET image 5 cm above the orbito-meatal line at 33 min after injection. The percent of the injected activity going to the brain was calculated for an assumed brain weight of 1400 g.

A typical brain time-activity curve was selected and fitted by eye to the function

$$A_{BR}(t) = A_{BR}(1 - e^{-kt}), \quad (2)$$

where $A_{BR}(t)$ and A_{BR} were the amounts of activity in brain at time t after injection and at 33 min, respectively. We determined k to be 5.2/hr. This value of k gives a half-time for uptake of 8 min and a 95% uptake time of 35 min, justifying the use of Eq. (2) for the cerebral time-activity curve. The cumulated activity of the brain, A_{BR} (μCi-hr), is given by

$$\tilde{A}_{BR} = \frac{k}{\lambda(k + \lambda)} A_{BR}, \quad (3)$$

where λ is the decay constant of F-18 (0.382/hr) and k and A_{BR} are defined above [see Eq. (2)]. This expression represents the combined effects of uptake and radioactive decay.

F-18 uptake for other organs. The average tissue distributions in two dogs (*5*) at 60 min after intravenous injection (see Table 1) were used to calculate radiation doses for all the organs except for red marrow, testes, bladder, and brain. The percentages of injected activity in red marrow and testes were estimated from their relative weights. Total-body uptake, exclusive of the other organs, was assumed to be 70% of the injected activity. It was assumed that these 60-min distributions were present instantly after injection and that the effective half-time was 1.83 hr ($T_{1/2}$ of F-18) for all organs except the bladder and the brain.

Radiation dosimetry calculations. The MIRD 'S' values (*7*) were used for the calculation of radiation dose to the bladder wall and all the organs except for the brain and the heart. For these two, 'S' values were calculated (*7*) from absorbed fractions (*8*), equilibrium dose constants (*9*), and masses. Calculations were carried out to at least three significant figures, but means are rounded off to two significant figures because of the two-figure 'S' values.

The formula used to calculate the dose to the bladder wall, D_{BW}, in rads is

$$D_{BW} = 1.1\, S_{BW \leftarrow BC}\, \tilde{A}_{BC} + S_{BW \leftarrow TB}\, \tilde{A}_{TB}, \quad (4)$$

where the 'S' values (rad/μCi-hr) are from MIRD pamphlet No. 11 (*7*), the $\tilde{A}$ (μCi-hr) are cumulated activities, and the subscripts BW, BC, and TB refer to bladder wall, bladder contents, and total body. The

TABLE 1. ORGAN F-18 ACTIVITY FROM INTRAVENOUS FDG(F-18)

Organ	% Injected activity/organ
Kidneys	0.80
Lung	2.4
Liver	3.2
Spleen	1.2
Red marrow	1.5
Ovaries	0.01
Testes	0.03
Heart	3.5
Total body	70

Based on Gallagher et al. (*5*) except for total body (see text) and red marrow and testes (estimates based on relative weight: 1.5% of injected activity to red marrow and 0.03% to testes).

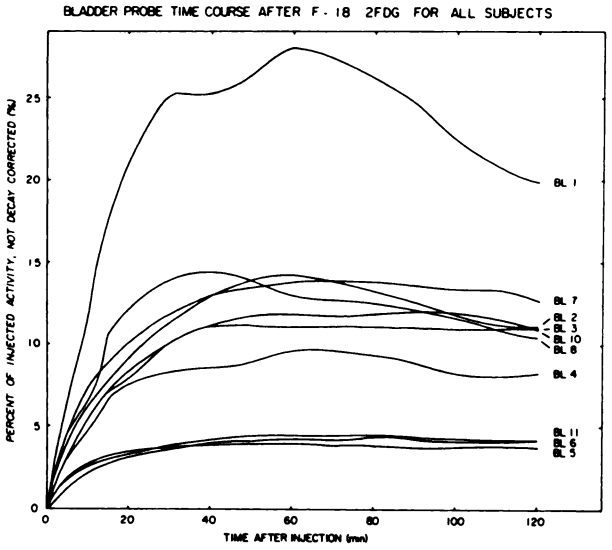

FIG. 1. Ten time-activity courses from collimated NaI(Tl) probe plotted as a percent of injected activity, decay included. Area R under these curves is proportional to cumulated activity $\tilde{A}_{BC}$. Height H of curve at 120 min is proportional to amount of F-18 activity in bladder (A_{BC}) at 120 min.

factor 1.1 in Eq. (4) accounts for the 10% additional amount of F-18 cleared to the bladder between 2 and 4 hr after injection. This factor is determined in Table 3 as described above. Radiation doses to all organs except for the bladder wall were calculated using

$$D_i = S_{i \leftarrow i} \tilde{A}_i + S_{i \leftarrow TB} \tilde{A}_{TB} + S_{i \leftarrow BC} \tilde{A}_{BC}, \quad (5)$$

where D_i is the dose (rad) to organ i, and the other terms and subscripts are as defined above.

RESULTS

Bladder activity and radiation dosimetry. The bladder time-activity curves for the ten subjects are plotted in Fig. 1. The shapes of the ten curves are similar. Table 2 shows the results of the 2-hr bladder activity determinations from the measurement of aliquots of a complete urine sample in the ten subjects. The mean percent of injected activity at 2 hr, decay-corrected to injection time, is 20.6% with a standard error of 3.3%.

The amount of F-18 activity in the bladder at 4 hr, after a 2-hr void, is expressed as a percent of 2-hr activity in Table 3 for two subjects. The additional activity in the bladder is 10% with decay included. The effect of this additional activity is taken into account when the absorbed radiation dose to the bladder wall is calculated [see Eq. (4)].

The radiation doses to the bladder wall for the ten subjects are shown in Table 2 along with the cumulated activities. The mean bladder-wall dose for ten subjects for a 2-hr void, including 4-hr data, is 440 mrad/mCi, with a standard error of 76.

The bladder time-activity data were used to calculated radiation doses to the bladder wall for void times between 1 and 2 hr. This was done by using the data collected for each subject to calculate the radiation dose to the bladder wall at three void times—60, 80, and 100 min—in addition to 120 min. The mean radiation dose at these four times was determined. If the subjects were allowed to void at 1 hr, the bladder-wall dose would be reduced to 50% of the 2-hr dose, or 220 mrad/mCi (see Fig. 2).

TABLE 2. RADIATION DOSE TO THE BLADDER WALL FROM INTRAVENOUS 2FDG(F-18)

Subject	Activity in bladder at two hours % injected activity†	Cumulated activity* (μCi-hr)	Bladder dose (mrad/mCi)
1	41.6	450	934
2	24.3	234	506
3	23.8	197	433
4	17.7	160	360
5	8.03	71.7	185
6	8.91	74.6	190
7	27.3	240	518
8	22.4	257	552
10	23.1	221	480
11	8.73	75.7	192
Mean	20.6		440
s.e.	3.3		76

* For injection of 1 mCi.
† Decay-corrected to injection time.

Brain uptake and radiation dosimetry. The percent of injected activity, and the radiation doses to the brain from 2FDG(F-18), are shown in Table 4 for eight subjects. The mean percent of injected activity to the brain is 3.9% with a standard error of 0.52%. The mean dose ± s.e. to the brain for these subjects is 81 ± 7 mrad/mCi.

Radiation dose to other organs. The radiation doses to other organs, and to the bladder and brain, are presented in Table 5. The doses to all organs except for spleen, bladder, and heart are between 50 and 85 mrad/mCi. The doses to spleen, heart, and total body are 160, 160, and 39 mrad/mCi, respectively.

TABLE 3. F-18 ACTIVITY IN BLADDER 4 HR AFTER INTRAVENOUS FDG(F-18)

Subject	Percent of 2-hr activity
3	9.4
7	11.
Mean	10.

TABLE 4. RADIATION DOSE TO BRAIN FROM INTRAVENOUS 2FDG(F-18)

Subject	Activity in brain at 33 min, % injected activity†	Cumulated activity* (μCi-hr)	Radiation dose (mrad/mCi)
1	4.32	105	80.5
2	5.66	138	101
5	5.57	136	99.2
6	3.13	76.5	62.9
7	5.39	132	96.5
8	3.11	75.8	62.5
9	4.96	121	90.1
10	2.43	59.2	52.4
Mean	3.95		81
s.e.	0.5		7.2

* For injection of 1 mCi.

† Decay-corrected to injection time.

DISCUSSION

The measurement of the cerebral utilization rate of glucose with PET and 2FDG(F-18) has proved useful in the study of the normal and diseased brain. This study shows that the radiation dose to the critical organ from the use of 2FDG(F-18) is not excessive.

Bladder activity. As shown in Fig. 1 and Table 2, the subjects fall into three groups showing different ranges of percent injected activity in the bladder. For one group of three, the percent injected activity in the bladder at 2 hr is ~9%. Another group shows ~23% injected activity in the bladder. Bladder activity (42%) of Subject 1 is over two standard deviations higher than the mean for the other subjects, but this individual was included in the data base because doing so leads to a conservative estimate of the radiation dose. The variability in bladder activity could be due to differences in the tubular reabsorbtion of 2FDG(F-18) (*4*). The variability is not correlated ($p > 0.05$) with age or weight of a subject.

Brain uptake. The radiation dose to the brain (81 mrad/mCi) is similar to the radiation doses for other organs.

Bladder dosimetry. The bladder is the critical organ for the administration of 2FDG(F-18). For 5 mCi injected, the bladder wall receives a radiation dose of 2.2 rad with a 2-hr void. If the void time is decreased to 1 hr, the dose is reduced to 50% or 220 mrad/mCi (see Fig. 2). Note that the radiation dose estimates to the bladder wall are based on a reference man with a bladder size fixed at 200 g for contents and a bladder wall of 45 g.

Comparison of the results obtained in this study with the radiation dosimetry presented by Brownell et al. (*6*) is not possible without a more detailed description of the methods and calculations used to obtain their result of 144 mrad/mCi to the bladder wall.

Reivich et al. (*2*) presented a value of 289 mrad/mCi for the bladder dose as calculated by the earlier MIRD method (*8*), which has undergone changes for organs with walls, such as the bladder (*7*). The present work uses the more recent MIRD method.

Note that the available animal data (*5*) do not allow a realistic estimate of the radiation dose to the human bladder wall without assuming a time-activity curve.

Recommendations for obtaining low radiation doses to the bladder wall. Several strategies can be used to reduce the radiation dose to the bladder wall. One would

TABLE 5. RADIATION DOSE FOR INTRAVENOUS 2FDG(F-18) TO VARIOUS ORGANS

Target organ	Activity per organ (μCi/organ*)	From target organ (mrad/mCi)	From total body (mrad/mCi)	From bladder (mrad/mCi)	Total dose to target organ (mrad/mCi)
Kidneys	8	46.5	37.0	1.18	85
Lungs	25	40.9	35.1	1.52	78
Liver	30	37.2	37.1	0.887	75
Spleen	12	120.	37.1	0.718	160
Red marrow	15†	12.3	35.1	3.84	51
Ovaries	0.1	13.7	37.0	1.90	53
Testes	0.3†	13.5	38.8	15.6	68
Bladder‡	—	—	—	—	440
Brain‡	—	—	—	—	80
Heart	36	134	24.1	—	160
Total body	700	—	33.3	5.9	39

* Based on 1 mCi injection for percent injected activity from Table 1.

† Estimate based on relative weight: 1.5% of dose to red marrow and 0.03% of dose to testes.

‡ The radiation dose to the brain and to the bladder wall for 2-hr void time were evaluated in humans. See Tables 2 and 4.

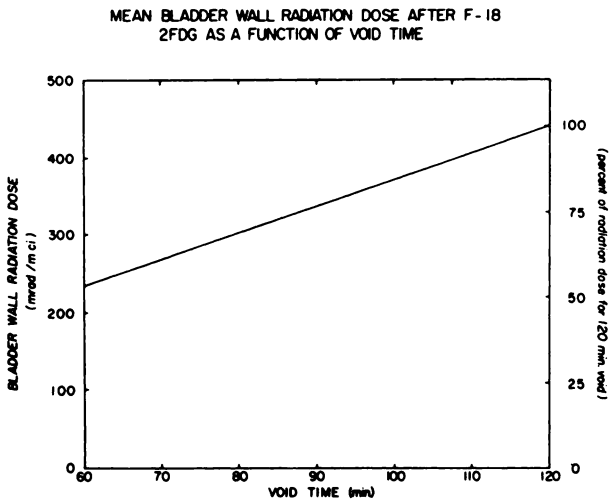

FIG. 2. Reduction in absorbed radiation dose to bladder wall resulting from void times between 60 and 120 min. Bladder-wall dose was calculated for each subject for assumed void times of 60, 80, and 100 min in addition to 120 min. Mean radiation dose was then plotted at the four void times and connected with a smooth curve, in this case a straight line. Left- and right-hand scales give mean radiation dose (mrad/mCi) to bladder wall and percent of dose for a 2-hr void time, respectively. Radiation dose is reduced to 50% by reducing void time from 120 to 60 min.

be to void at an earlier time. The effect of this is demonstrated in Fig. 2. This reduces the dose because it removes the source of activity. Another strategy would be to maximize the subject's bladder volume during the study. Because the radiation dose to the bladder wall is proportional to the concentration in the bladder, a small bladder volume would result in a larger dose and larger volume would result in a smaller dose. Thus, the bladder-wall dose would be lowered if the subject's bladder was as full as possible during the study.

CONCLUSION

The 2-fluoro-deoxyglucose technique for the measurement of cerebral metabolic rate is dependent upon a rapidly falling arterial concentration curve after a bolus intravenous injection. This falling curve is due in part to the ability of the kidney to clear the substance from the blood and to excrete it into the bladder.

This measurement of the radiation dose to the critical organ for 2FDG(F-18) suggests a limit for the amount of activity that can be injected in the quest for increased spatial resolution with PET and avoids the assumptions made in using animal biodistribution data for human dosimetry calculations.

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