Estimation of the Radiation Dose in Man Due to 6-[^{18}F] Fluoro-L-Dopa

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The radiation dose to the organs of the human body after an intravenous administration of 6-[^{18}F] fluoro-L-dopa was estimated using the recommendations of the International Committee on Radiological Protection (ICRP). The bladder wall received the highest dose, 6.95E-10 Sv/Bq (2,600 mrem/mCi), and as a consequence the dose to the genitalia was 1.6E-11 Sv/Bq (60 mrem/mCi). The major organs received a dose of 5.66E-12 to 1.87E-11 Sv/Bq (20 to 60 mrem/mCi). The effective dose equivalent was estimated at 5.39E-11 Sv/Bq (200 mrem/mCi).

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The tracer 6-[^{18}F] fluoro-L-dopa and positron emission tomography have been used to visualize the intracerebral distribution of the neurotransmitter dopamine in humans (*1*) and a reduced accumulation of 6-[^{18}F] fluorodopamine has been demonstrated in the basal ganglia of patients suffering from Parkinson's disease (*2,3*). In the future 6-[^{18}F] fluoro-L-dopa will probably be used to measure intracerebral dopamine metabolism in a wide variety of patients particularly those with extra pyramidal movement disorders or mental disturbances such as schizophrenia. We have, therefore, estimated the radiation dose to man due to 6-[^{18}F] fluoro-L-dopa. The estimation is based on the whole-body distribution of fluorine-18 (^{18}F) in dogs which had been given 6-[^{18}F] fluoro-L-dopa, and the time-activity curve of ^{18}F in the blood and urine of humans who had also received labeled dopa.

MATERIALS AND METHODS

Whole-body distribution of 6[^{18}F] fluoro-L-dopa in dogs

Two mongrel dogs (male, 17.3 kg; female, 21.7 kg) were anesthetized with phenobarbital. Each was then given ~1 mCi (37 MBq) 6-[^{18}F] fluoro-L-dopa (181 mCi/mmol) (*4*) intravenously. The dogs were killed at 1 and 2 hr, respectively, and dissected. Aliquots from each organ were weighed and assayed for ^{18}F in a NaI (Tl) well-type scintillation counter. An aliquot of the dose of 6-[^{18}F] fluoro-L-dopa was diluted in 1 l and used as standard. All samples were counted in the same geometry. After correction for radioactive decay the percentage of the dose per gram of tissue was calculated.

Disappearance of ^{18}F from blood and appearance of ^{18}F in the urine of man after i.v. 6-[^{18}F] fluoro-L-dopa

Nine informed male volunteers (25–49 yr) were studied. Each was given 0.5 mCi 6-[^{18}F] fluoro-L-dopa intravenously. Samples of venous blood were taken up to 1 hr and urine was collected up to 6.5 hr. The ^{18}F content of aliquots of whole blood was measured.

Calculation of radiation dose

The method used to calculate the radiation doses is that recommended in International Committee on Radiological Protection ICRP-30 and its supplements (*5*).

This method requires that the number of nuclear transformations in each organ be calculated. For gamma rays each organ then acts as a source for all other organs. Using the energy absorbed per gram in a target organ per transformation in a source organ (the specific effective energy), the gamma dose to each organ can be calculated. For beta particles, the ICRP gives the fraction of the energy absorbed by various target organs such as the gastrointestinal (GI) tract and bone surfaces from source organs.

From Table 1 we see that the ^{18}F is relatively uniformly distributed throughout all organs and tissues with the exception of the liver, spleen, and pituitary. From Table 2 we know that one-half of the ^{18}F injected collects in the bladder; the other half is distributed throughout the body. For the purposes of the calculation it is assumed that this distribution was achieved immediately after the administration of 6-

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TABLE 1
Distribution of ^{18}F in the Tissues of Dogs After Intravenous Injection of 6-[^{18}F] Fluoro-L-Dopa

Organ tissue	Percent relative concentration of ^{18}F in tissue* 1 hr	2 hr
Liver	131	67
Spleen	112	34
Kidney	73	65
Muscle, skeletal	52	32
Muscle, smooth		26
Heart	51	31
Lung	59	56
Blood	32	30
Bone	16	16
Skin	35	32
Thymus	65	54
Adrenal	66	59
Pancreas	43	33
Testes	57	
Thyroid	50	30
Pituitary	283	220
Brain, cortex	38	45
Brain, striatum	63	68
Brain, thalamus	41	34
Brain, cerebellum	61	57

* Percent relative concentration = $\dfrac{\frac{^{18}F \text{ in tissue, cpm}}{\text{wt of tissue, g}}}{\frac{^{18}F \text{ injected, cpm}}{\text{body weight, g}}} \times 100$

[^{18}F]fluoro-L-dopa. However, Table 1 shows that radioactivity in the liver and spleen actually fell with a half-time of ~1 hr and so it was assumed that the instantaneous concentration in these organs would have been twice that measured at 1 hr. In other words, the initial concentration of ^{18}F in the liver and spleen was four times that in the other organs.

To calculate the quantity of radioactivity initially in each organ we let m(i) be the weight of organ i and c the average concentration of ^{18}F within the body [excluding liver, spleen and bladder (Tables 1, 2)]. Then, because only half of the dose of ^{18}F is retained, for a 1Bq injection,

$$0.5 = 4c\ m(\text{liver}) + 4c\ m(\text{spleen}) + c\ m(\text{rest of body})$$
$$= 4c\ 1800 + 4c\ 180 + c(70{,}000 - 1{,}800 - 180)$$
$$c = 6.58 \times 10^{-6}\ \text{Bq/g}.$$

The initial activity in the liver is

$$4 \times 1800 \times c = 4.74 \times 10^{-2}\ \text{Bq};$$

the initial activity in the spleen is

$$4 \times 180 \times c = 4.74 \times 10^{-3}\ \text{Bq};$$

and the rest of the body contains

$$(70{,}000 - 1{,}800 - 180)c = 0.448\ \text{Bq}.$$

Knowing the initial injected activity in each tissue or organ, the number of transformations that take place in the organ for the initially injected activity of 1 Bq can be calculated.

For the liver and the spleen which have the same effective decay constant

$$\left(\lambda_e = \frac{0.693}{110 \times 60} + \frac{0.693}{60 \times 60} = 2.98 \times 10^{-4}\ s^{-1}\right),$$

where the number of transformations are 159 and 15.9, respectively. For the rest of the body the effective decay constant is based solely on the physical decay of ^{18}F and is $1.05 \times 10^{-4}\ s^{-1}$ so that the number of transformations is 4,260. For the bladder the initial activity is 0.5 Bq per unit administered. Until the bladder is emptied the effective decay constant is due to ^{18}F decay. Assuming that 80% of the bladder activity was voided at 2 hr the number of transformations that took place in the bladder is 2,980.

When the number of transformations in each source organ is multiplied by the specific effective energy the gamma dose to each target organ is obtained. To use the total body as a source rather than the rest of the body, the formulation described in ICRP-30, Appendix 1, was used for the number of transformations occurring in each organ.

Specific effective energy is the product of the specific absorbed fraction, given in ICRP-23, in MeV the energy of the radiation (0.511 MeV), the yield of the radiation (1.94), the quality factor (1) and 1.6×10^{-10} to convert MeV/g to J/kg.

To calculate the beta dose to each organ the average beta energy of ^{18}F was taken to be 0.244 MeV (ICRP-2). For the whole body the beta dose is given by:

$$\frac{4{,}260}{70{,}000} \times 0.244 \times 1.6 \times 10^{-10} = 2.38 \times 10^{-12}\ \text{Sv}.$$

Because the liver and spleen have concentrations greater than average, an additional beta dose must be calculated due to this excess; it amounts to 9.98×10^{-13} Sv for each organ.

The pituitary also has a higher than average concentration of ^{18}F. It receives 1.22×10^{-11} Sv.

The beta dose to the bladder wall due to transformations that took place in the urine in the bladder amounts to 5.68×10^{-10} Sv. The model used in this calculation was the same as that recommended by ICRP-30 for the case of the GI tract.

Table 3 summarizes the results of all the preceding calcula-

TABLE 2
^{18}F in Urine of Man After Intravenous Injection of 6-[^{18}F] Fluoro-L-Dopa

Subject	Interval over which urine was collected (hr)	% dose ^{18}F recovered
1	0–2	39
2	0–2	41
3	0–2.5	43
4	0–3	48
5	0–3	48
6	0–3.5	50
7	0–4	50
8	0–3	45
	3–3.5	9
	3.5–6.5	5

TABLE 3
Estimation of the Radiation Dose to Various Organs of the Human Body After Intravenous Administration of 6-[^{18}F] Fluoro-L-Dopa

Total dose in sieverts per Bq

Target organ	Source organ: Bladder contents	Liver	Spleen	Total body	Sum
Bladder wall	6.89E-10	8.83E-15	3.30E-16	6.78E-12	6.95E-10
Stomach wall	5.18E-13	4.74E-14	2.47E-14	6.71E-12	7.30E-12
Small intestine	4.23E-12	3.97E-14	3.48E-15	7.17E-12	1.14E-11
Upper large intestine	3.85E-12	6.45E-14	3.51E-15	7.13E-12	1.11E-11
Lower large intestine	1.15E-11	8.17E-15	1.76E-15	7.19E-12	1.87E-11
Kidney	6.27E-13	9.41E-14	2.14E-14	6.65E-12	7.39E-12
Liver	4.60E-13	1.64E-12	2.69E-15	6.60E-12	8.71E-12
Lungs	7.77E-14	6.00E-14	5.52E-15	6.16E-12	6.30E-12
Muscle	2.89E-12	2.81E-14	3.70E-15	5.89E-12	8.81E-12
Ovaries	1.02E-11	4.76E-15	2.70E-15	6.50E-12	1.67E-11
Pancreas	4.20E-13	1.21E-13	4.89E-14	6.57E-12	7.16E-12
Skeleton	9.56E-13	1.85E-14	1.93E-15	6.02E-12	7.00E-12
Red marrow	2.04E-12	2.71E-14	2.85E-15	6.39E-12	8.46E-12
Skin	1.06E-12	1.52E-14	1.59E-15	4.59E-12	5.66E-12
Spleen	3.67E-13	2.51E-14	1.33E-12	6.72E-12	8.44E-12
Testes	8.24E-12	2.86E-15	2.41E-16	6.95E-12	1.52E-11
Thymus	5.18E-14	3.39E-14	1.20E-15	6.07E-12	6.15E-12
Thyroid	1.54E-14	4.61E-15	3.72E-16	5.87E-12	5.89E-12
Pituitary	1.54E-14	4.61E-15	3.72E-16	1.56E-11	1.57E-11
Uterus	2.41E-11	1.11E-14	1.17E-15	6.59E-12	3.07E-11
Total body	3.03E-12	4.28E-14	4.25E-15	5.89E-12	8.97E-12

Total dose in mrem per mCi

Target organ	Source organ: Bladder contents	Liver	Spleen	Total body	Sum
Bladder wall	2,548	0	0	25	2,573
Stomach wall	2	0	0	25	27
Small intestine	16	0	0	27	42
Upper large intestine	14	0	0	26	41
Lower large intestine	43	0	0	27	69
Kidney	2	0	0	25	27
Liver	2	6	0	24	32
Lungs	0	0	0	23	23
Muscle	11	0	0	22	33
Ovaries	38	0	0	24	62
Pancreas	2	0	0	24	27
Skeleton	4	0	0	22	26
Red marrow	8	0	0	24	31
Skin	4	0	0	17	21
Spleen	1	0	5	25	31
Testes	31	0	0	26	56
Thymus	0	0	0	22	23
Thyroid	0	0	0	22	22
Pituitary	0	0	0	58	58
Uterus	89	0	0	24	113
Total body	11	0	0	22	33

tions. It gives the sum of the beta and gamma doses to each organ or tissue.

In order to compare the risk due to irradiation from an injection of 6-[^{18}F]fluoro-L-dopa the concept of the effective dose equivalent was used. ICRP defines the effective dose equivalent

$$H_E = \Sigma W_T H_T,$$

where W_T is a weighting factor representing the proportion of the stochastic risk resulting from irradiation of tissue T to the total risk when the whole body is uniformly irradiated and H_T is the mean dose equivalent to tissue T. By this formulation doses are placed on a common risk scale whether the dose is

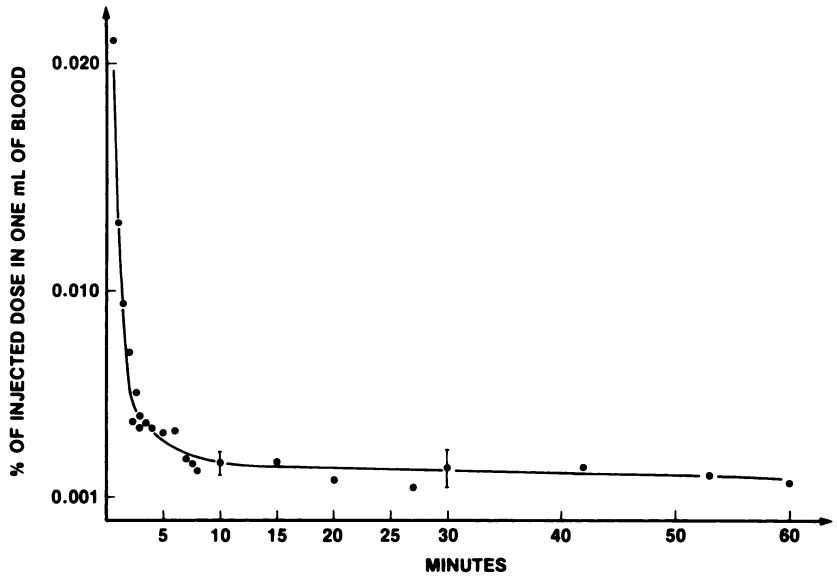

FIGURE 1
Disappearance of ^{18}F from blood of humans after i.v. administration of 6-[^{18}F] fluoro-L-dopa

non-uniform or uniform. As suggested in ICRP-42, the weighting factors for gonads, breast, red bone marrow, lung, thyroid and bone surfaces are assigned their standard weights. A weight of 0.06 is assigned to the remaining five organs receiving the maximum dose. The dose to the breast is taken to be the dose to muscle, and the dose to the gonads is the higher of the dose to the testes and ovaries. Based on the results of Table 3

$$\begin{aligned} H_E = {} & (0.25)(\text{ovaries}) + (0.15)\,\text{muscle} + \\ & (0.12)(\text{red bone marrow}) + \\ & (0.12)(\text{lung}) + (0.03)(\text{thyroid}) + \\ & (0.03)\text{bone surfaces} + (0.06)\,\text{bladder wall} + \\ & (0.06)(\text{uterus}) + (0.06)(\text{pituitary}) + \\ & (0.06)(\text{lower large intestine}) + \\ & (0.06)(\text{small intestine}) \\ = {} & 5.39 \times 10^{-11}\ \text{Sv per Bq intake.} \end{aligned}$$

In non SI units this corresponds to 200 mrem per mCi intake, i.e., 1 mCi 6-[^{18}F]fluoro-L-dopa results in the same detriment to an individual as a uniform whole-body irradiation dose of 200 mrem.

DISCUSSION

In any estimate of radiation dosimetry certain assumptions have to be made. In the present case it is assumed that, except for spleen, liver, and bladder the effective half-life of 6-[^{18}F] fluoro-L-dopa in the whole body is the physical half-life of ^{18}F, 1.83 hr. It is further assumed that the bladder is emptied after 2 hr, at which time 80% of the radioactivity passing through it will be eliminated. It is also assumed that the whole-body distribution of ^{18}F at 1 hr represents that which would have occurred at zero time. The rapid removal of ^{18}F from the blood, Fig. 1, supports the last assumption.

The radiation dose to the bladder is ten times greater than that received by any other organ or tissue. However, this irradiation can be reduced considerably by having the patient adequately hydrated and ensuring that he voids as soon as possible after the injection. Thereafter, the amount of ^{18}F excreted through the kidneys is small and will contribute little to the overall irradiation received by the bladder.

It will be noted from Table 3 that after the bladder the genitalia receive the biggest dose of irradiation. Most of this is due to gamma irradiation from the bladder and can be reduced by minimizing the amount of radioactive urine retained during the first 2 hr of a study. Compared to 2-[^{18}F] fluoro-2-deoxy-D-glucose (6) the radiation dose to most organs per mCi of 6-[^{18}F] fluoro-L-dopa injected is less. This is probably because a half rather than only a quarter of the ^{18}F given is excreted in the urine during the first 2 hr of a study. Because of this differential excretion the radiation dose to the bladder from 6-[^{18}F] fluoro-L-dopa exceeds that from 2-[^{18}F]fluoro-2-deoxy-D-glucose.

Finally, the effective dose equivalent (EDE) was calculated to be 5.39×10^{-11} Sv/Bq(200 mrem/mCi). When a tomograph of efficiency similar to that built at this institution (7) is used good quality images of the basal ganglia are obtained in 5–10 min 1 hr after an i.v. injection of 2 mCi (74 MBq) 6-[^{18}F]fluoro-L-dopa. In other words, a single measurement of intracerebral dopamine metabolism will give the radiation dose similar to the limit recommended for the general public, 500 mrem, and one-tenth that advised for radiation workers. Our estimate of the irradiation dose is falsely high because it does not take the short biological half-life of 6-[^{18}F]fluoro-L-dopa into account. It would thus be considered reasonable to repeat a study in any 1 yr and to neglect small increases in the dose of irradiation that might accrue from pharmacological manipulations that alter the distribution and retention of dopa or its

metabolites. We recognize that comparisons with dose limitations designed for radiation workers is not recommended for medical exposures but we believe that 6-[^{18}F]fluoro-L-dopa will be used widely as a tracer in clinical research with volunteers and, therefore, doses have been put in context.

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