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Radiation Dosimetry of ^{18}F-FPEB in Humans

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^{18}F-3-fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile (^{18}F-FPEB) is a potent and specific radioligand for the metabotropic glutamate receptor subtype 5 (mGluR5). Before undertaking clinical research studies with ^{18}F-FPEB, we performed studies of human radiation dosimetry. **Methods:** Serial whole-body scans were obtained in 9 healthy human subjects (5 men, 4 women) for 190–440 min after the intravenous administration of ^{18}F-FPEB. Radiation doses were estimated using the OLINDA/EXM software. **Results:** Peak organ doses were to the urinary bladder wall, 0.258 mGy/MBq (0.955 rad/mCi), and gallbladder wall, 0.193 mGy/MBq (0.716 rad/mCi). The effective dose was 0.025 mSv/MBq (0.0922 rem/mCi). The doses to the red marrow and spleen were 0.00797 mGy/MBq (0.0295 rad/mCi) and 0.00709 mGy/MBq (0.0262 rad/mCi), respectively. Reducing the urinary voiding interval to 60 or 90 min lowered the urinary bladder wall dose to 0.0885 mGy/MBq (0.327 rad/mCi) or 0.128 mGy/MBq (0.473 rad/mCi), respectively, and the effective dose to 0.0149 mSv/MBq (0.0551 rem/mCi) or 0.0171 mSv/MBq (0.0634 rem/mCi), respectively. **Conclusion:** Urinary voiding should be performed during ^{18}F-FPEB studies to minimize radiation exposure to research subjects.

Key Words: ^{18}F-FPEB; glutamate; mGluR5; radiation dosimetry

J Nucl Med 2014; 55:1119–1121
DOI: 10.2967/jnumed.113.133843

The metabotropic glutamate receptor subtype 5 (mGluR5) is a type I metabotropic glutamatergic receptor, which is an important modulator of both *N*-methyl-D-aspartate and dopamine receptor signaling; it positively modulates *N*-methyl-D-aspartate receptor function and has complex interactions with dopamine receptor intracellular signaling (*1,2*). Altered function of the mGluR5 has been implicated in the pathophysiology of several neurologic and psychiatric disorders including Fragile X syndrome (*3*), Huntington and Parkinson disease (*4,5*), psychostimulant drug and alcohol abuse (*6–8*), depression, and anxiety as well as being involved in learning and memory (*9–12*). ^{18}F-3-fluoro-5-[(pyridin-3-yl)ethynyl] benzonitrile (^{18}F-FPEB) is a promising radioligand for imaging the mGluR5 in humans. It has a high affinity (0.11–0.15 nM) for the mGluR5 and nearly optimal lipophilicity for imaging, with a logP of 2.8 (*13*). Initial human imaging studies have shown high contrast between regions rich in mGluR5 levels, such as the anterior cingulated, and regions with low levels, such as the cerebellum and pons, as well as the ability to estimate regional receptor levels using both bolus administration with 2-tissue-compartment modeling and bolus–infusion administration (*14,15*). Given the importance of the mGluR5 in several disease states and its promise as a PET radioligand for studies of mGluR5, we undertook studies of human radiation dosimetry of ^{18}F-FPEB.

MATERIALS AND METHODS

After approval of this study by the appropriate institutional review boards (IRBs), all subjects provided written informed consent before enrollment. All subjects had to be 18 y or older and have a normal medical history, physical examination, and laboratory testing including a comprehensive metabolic panel, complete blood panel with differential, urine analysis, negative urine drug screens, and a normal electrocardiogram. A history of significant medical condition, psychiatric disorder including any history of drug abuse or eating disorder, pregnancy, and lactation were exclusion criteria. Nine healthy subjects (5 men and 4 women; mean age, 23.7 y; age range, 18–47 y) were studied after intravenous bolus administration of ^{18}F-FPEB (mean dose, 173 MBq [4.67 mCi]; dose range, 160–187 MBq [4.34–5.05 mCi]). Seven of the 9 subjects were studied at Vanderbilt after approval by the Vanderbilt IRB using a Discovery DTSE PET/CT scanner (GE Healthcare) and were scanned for 190 min after administration of ^{18}F-FPEB. Serial whole-body images were obtained from the top of the head to the mid thigh. Two subjects were studied at the Institute for Neurodegenerative Disorders after approval from the New England IRB using an ECAT EXACT HR+ PET scanner (Siemens) and were scanned for 382 and 440 min after ^{18}F-FPEB administration using serial whole-body acquisitions from the top of the head to the mid thigh. For the calculation of radiation dosimetry, regions of interest were drawn around regions representing major organs at all time points with appropriate decay corrections. The resultant region-of-interest data were fit to time–activity curves using the SAAM II software (SAAM Institute, University of Washington) (*16*). Time–activity curves were integrated and time–activity integrals entered into the OLINDA/EXM (Vanderbilt University) software (*17,18*); organ dose estimates and effective dose values were obtained using the most appropriate anthropomorphic model for each subject. Urine excretion was modeled using the dynamic bladder model provided in the OLINDA/EXM code.

RESULTS

Organ residence times for ^{18}F-FPEB are shown in Table 1. The calculated radiation dose estimates are shown in Table 2. When urinary voiding at 3.5 h after^{18}F-FPEB administration was used, the highest organ doses were to the urinary bladder wall (0.258 mGy/MBq [0.955 rad/mCi]) and the gallbladder wall (0.193 mGy/MBq [0.716 rad/mCi]). The highest doses to blood-forming organs were to the red marrow (0.00797 mGy/MBq [0.0295 rads/mCi])

Received Oct. 31, 2013; revision accepted Feb. 26, 2014.
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Published online May 5, 2014.
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TABLE 1
Mean Organ Residence Times (±SD) for ^{18}F-FPEB with Urinary Voiding at 3.5 Hours

Organ	Mean residence time
Brain	0.116 ± 0.0546
Gallbladder contents	0.114 ± 0.127
Upper large intestine	0.0829 ± 0.0309
Small intestine	0.151 ± 0.0563
Lower large intestine	0.0152 ± 0.00565
Liver	0.120 ± 0.0496
Urinary bladder contents	0.531 ± 0.276
Remainder	1.070 ± 0.239

Data are MBq-hr/MBq or μCi-hr/μCi administered.

and spleen (0.00709 mGy/MBq [0.0262 rad/mCi]). The highest gonadal dose was to the ovaries (0.0185 mGy/MBq [0.0684 rad/mCi]). The effective dose was 0.025 mSv/MBq (0.0922 rem/mCi). Reducing the urinary bladder voiding interval to 60 or 90 min produced significant decreases in the dose to the urinary bladder wall, lowering absorbed doses to 0.0885 mGy/MBq (0.327 rad/mCi) for 1-h voiding and 0.128 mGy/MBq (0.473 rad/mCi) for 1.5-h voiding. Decreases were also seen in the effective dose, with reductions to 0.0149 mSv/MBq (0.0551 rem/mCi) for 1-h voiding and 0.0171 mSv/MBq (0.0634 rem/mCi) for 1.5-h voiding. Smaller decrements were seen in doses to the ovaries and red marrow, but the dose to the gallbladder wall was virtually unchanged.

DISCUSSION

The results of the current study indicate that multiple 185-MBq (5-mCi) doses of ^{18}F-FPEB can be administered for studies of cerebral mGluR5 in humans. To minimize the radiation dose received by human subjects, it is recommended that bladder voiding be done at 1 or 1.5 h after bolus administration of ^{18}F-FPEB, which significantly lowers both the urinary bladder wall and the effective doses. Previous studies indicate that 1.5 h of imaging after bolus injection of ^{18}F-FPEB should allow quantitation of mGluR5 levels in all brain regions; for such studies, urinary voiding at the end of the imaging study is recommended (*14,15*).

In comparing the present study with a recently published study of radiation dosimetry (*14*), the greatest difference between the previous and the current radiation dosimetry studies is the dose to the urinary bladder wall, which is significantly higher in the current study. In the prior study, the dose to the urinary bladder wall

TABLE 2
Radiation Dosimetry for ^{18}F-FPEB with Urinary Voiding Intervals of 3.5, 1.5, and 1.0 Hours

	3.5-h voiding			1.5-h voiding			1.0-h voiding		
Organ	mGy/MBq	mrad/mCi	Coefficients of variation	mGy/MBq	mrad/mCi	Coefficients of variation	mGy/MBq	mrad/mCi	Coefficients of variation
Adrenals	0.00851	31.5	22.2	0.00839	31.1	23.2	0.00836	31.0	23.5
Brain	0.0204	75.5	37.2	0.0204	75.5	37.2	0.0204	75.4	37.1
Breasts	0.00480	17.8	21.9	0.00478	17.7	22.2	0.00477	17.7	22.3
Gallbladder wall	0.193	716	101.4	0.193	714	101.6	0.193	714	101.7
Lower large intestine wall	0.0249	92.1	20.7	0.0211	78.3	20.3	0.200	74.1	21.0
Small intestine	0.0428	159	26.3	0.0414	153	27.0	0.0410	152	27.3
Stomach wall	0.00882	32.7	17.2	0.00864	32.0	18.7	0.00858	31.8	19.2
Upper large intestine wall	0.0475	176	25.9	0.0465	172	26.5	0.0461	171	26.6
Heart wall	0.00690	25.5	22.2	0.00687	25.4	22.5	0.00687	25.4	22.6
Kidneys	0.00915	33.8	19.2	0.00892	33.0	20.8	0.00886	32.8	21.5
Liver	0.0203	75.1	32.6	0.0202	74.5	33.1	0.0201	74.4	33.2
Lungs	0.00603	22.3	22.3	0.00601	22.3	22.5	0.00601	22.2	22.6
Muscle	0.00821	30.4	5.0	0.00726	26.9	12.2	0.00698	25.8	14.9
Ovaries	0.0185	68.4	15.3	0.0150	55.7	12.2	0.0140	51.8	12.5
Pancreas	0.0102	37.8	26.8	0.0101	37.3	27.8	0.0100	37.1	28.2
Red marrow	0.00797	29.5	9.1	0.00735	27.2	14.2	0.00717	26.5	16.0
Osteogenic cells	0.00995	36.7	17.0	0.00957	35.4	19.5	0.00946	35.0	20.3
Skin	0.00530	19.6	13.1	0.00497	18.4	17.4	0.00487	18.0	18.9
Spleen	0.00709	26.2	18.5	0.00697	25.8	19.8	0.00693	25.6	20.2
Testes	0.0102	37.9	14.0	0.00772	28.6	3.6	0.00696	25.8	6.2
Thymus	0.00573	21.2	22.0	0.00571	21.1	22.1	0.00570	21.1	22.3
Thyroid	0.00851	31.5	23.2	0.00582	21.5	23.3	0.00582	21.5	23.3
Urinary bladder wall	0.258	955	50.1	0.128	473	47.1	0.0885	327	43.8
Uterus	0.0261	96.7	26.5	0.0180	66.5	15.5	0.0155	57.5	10.6
Total body	0.00922	34.1	7.4	0.00836	31.0	13.6	0.00810	30.0	15.8
Effective dose	0.0250*	92.2†	26.0	0.0171*	63.4†	14.3	0.0149*	55.1†	9.9

*mSv/MBq.
†mrem/mCi.
Coefficients of variation (ratio of SD to mean) are shown for each organ for each voiding interval.

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was 0.047 mGy/MBq (0.18 rad/mCi) versus 0.258 mGy/MBq (0.955 rad/mCi) in the current study. The reason for this difference may be the longer duration of scanning in the current study than in the previous study, 190–440 versus 90 min. The greater urinary bladder wall dose also produces a somewhat higher effective dose than reported in the previous study—that is, 0.025 mGy/MBq (0.0922 rad/mCi) without voiding versus 0.017 mGy/MBq (0.062 rad/mCi). Voiding at 90 min reduces the effective dose to virtually the same dose reported in the prior study and decreases the urinary bladder wall dose by more than 50%. With urinary voiding intervals of 1.0 or 1.5 h, the highest organ dose becomes the gallbladder wall, 0.193 mGy/MBq (0.714 rad/mCi), which is remarkably similar to the dose reported by Wong et al. (*14*), 0.19 mGy/MBq (0.71 rad/mCi).

CONCLUSION

The results of the current study demonstrate that ^{18}F-FPEB can be administered in doses to humans sufficient to allow quantitation of regional mGluR5 levels in brain. To minimize absorbed radiation doses, urinary voiding at 1 to 1.5 h is advocated to achieve the minimum reasonable dose, particularly for the urinary bladder wall and the effective dose.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This work was supported by a grant from the National Institute of Drug Abuse, 1R21 DA031441. No other potential conflict of interest relevant to this article was reported.

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J Nucl Med. 2014;55:1119-1121.
Published online: May 5, 2014.
Doi: 10.2967/jnumed.113.133843

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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