Human Dosimetry Estimates for the dopamine transporter radioligand [^{18}F]FECNT

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Introduction

[^{18}F] FECNT is a recently developed radioligand by Dr. Mark M Goodman at Emory University. It has potential applications in in-vivo quantitation of the dopamine transporter (DAT) using positron emission tomography (PET). The radiotracer is tailored specifically for observing changes in the amount of DAT found in the brain attributed to cocaine addiction, Parkinson's disease, and schizophrenia. This report provides the method and estimates for the human dosimetry with [^{18}F] FECNT based on whole-body PET imaging of nonhuman primates.

Experimental and Method

Radiopharmaceutical Preparation

[^{18}F] FECNT was synthesized by alkylation of 1-[^{18}F]fluoro-2-tosyloxyethane with 2β-carbomethoxy-3β-(4-chlorophenyl)nortropane. [^{18}F] FECNT was purified by high-performance liquid chromatography, to produce a product free from precursor.

Animal Subjects

Three male rhesus monkeys (body weight: ~10 kg) were initially immobilized with ketamine and then anesthetized with isoflurane (1.5%) for the duration of the scanning study. A urinary catheter was inserted and clamped so that the activity overlaying the bladder represented the total urinary excretion during scanning interval. Head of monkeys was placed in stereo tactic head holder and body laid in prone position. ECG, body temperature, heart and respiration rates were measured throughout the study.

PET image acquisition

Whole-body transmission and emission scans were acquired on a GE Advance tomograph (GE Medical Systems, WI). Prior to injection of the radioligand, each animal received a 40 min whole-body transmission scan from five sections of the body from head to knees with two rotating Germanium-68 rods for subsequent attenuation correction of the emission image. Three whole-body emission scans were performed following the intravenous administration of [^{18}F] FECNT 4.19, 4.90, 4.87mCi. Serial dynamic transaxial images were acquired for a total of 4 hours from five sections of the body from head to knees. Each bed position of the body was imaged 23 times, with the following sequence of frame acquisitions: 2 frames x 0.25 min; 3 frames x 0.50 min; 6 frames x 1 min; 5 frames x 2 min, 7 frames x 4 min.

Image and data analysis

Compressed planar images were analyzed with PMOD 2.5 (pixel-wise modeling computer software, PMOD Group, Zurich, Switzerland). Recovery of injected activity was calculated from five bed positions. Urinary bladder, brain, kidneys, liver, vertebrae, GI tract and lungs were easily identified on the emission images. Activity in vertebrae was assumed as red bone marrow. However, other organs, including spleen, thyroid and bone structures other than vertebrae, had inadequate activity to be identified on the emission images. A single generous region of interest was drawn on each organ that included all activity in the organ. Activity in "remainder of body" was calculated at each time point by subtracting that present in the identified source organs from recovered activity.

Activity in the source organs (not decay-corrected) were expressed as a percentage of injected dose and plotted versus time. The area under the time activity

curve of each organ was calculated with the trapezoidal method up to the last data acquisition at 240 min. To be conservative, the area under the curve from the last data acquisition (240 min) to infinity was calculated by assuming only physical decay ($T_{1/2}$ = 109.8 min) and no additional biological clearance. The area under the time activity curve of source organ from time zero to infinity is equivalent to residence time (h). The residence times from the monkey were converted to corresponding human values by multiplication with a factor to scale organ and body weights as follows:

$$\frac{\text{monkey body weight}}{\text{monkey organ weight}} \times \frac{\text{human organ weight}}{\text{human body weight}}$$

Average residence time calculated from three monkeys is shown in table 1.

Cumulative activity of [^{18}F] FECNT in urinary excretion was found to be less than10%. Due to the low activity in urinary bladder relative to the activity in surrounding tissues, exponential curve fitting was poor and the biological half life could not be calculated. Hence to be conservative, dosimetry was calculated without using the dynamic bladder model and assuming no urine voiding. Residence time of urinary bladder content was calculated in the same way as that of other organs. We observed substantial activity in GI tract that represents fraction excreted in small intestine and so GI tract model was implemented in MIRDOSE 3.1 software to calculate residence time in small intestine and large intestine. Organ absorbed doses were based on the MIRD scheme of a 70 kg human subject, using the residence times and GI tract model calculated above with MIRDOSE 3.1 computer program. Radiation doses to the organs are listed in table 2.

Comments on the report

The four organs with highest exposure (rad/mCi) were: kidneys (0.28), urinary bladder (0.19), lungs (0.16) and upper large intestine (0.14). Effective dose was 0.082 rem/mCi, which is close to the published data (0.058 rem/mCi) by Todd Deterding from Emory University Hospital (table 2). Because the dose to the testes was wrong in their paper, in the right column of Table 2, we recalculated organ doses using residence time in their paper. These differences may due to species difference or methodological discrepancies. In short, [^{18}F] FECNT showed a favorable profile of radiation burden that would allow repeated injections for research studies in human subjects.

Table 1: Residence times extrapolated to humans

Organ	Residence time (h)
Brain	0.18
Kidneys	0.11
Red Bone Marrow	0.10
Lungs	0.23
Liver	0.09
Urinary Bladder Content	0.09
Remainder of Body	1.41

Table 2: Human radiation dose estimates for [18F]FECNT

	NIMH	Recalculated Data (Emory University)
Organ	**rad/mCi**	**rad/mCi**
Adrenals	0.050	0.061
Brain	0.121	0.064
Breasts	0.030	0.051
Gallbladder Wall	0.053	0.062
LLI Wall	0.069	0.063
Small Intestine	0.135	0.066
Stomach	0.042	0.063
ULI Wall	0.147	0.065
Heart Wall	0.043	0.154
Kidneys	0.280	0.054
Liver	0.064	0.038
Lungs	0.166	0.046
Muscle	0.035	0.036
Ovaries	0.056	0.064
Pancreas	0.048	0.065
Red Marrow	0.061	0.060
Bone Surfaces	0.050	0.052
Skin	0.026	0.044
Spleen	0.044	0.048
Testes	0.032	0.051
Thymus	0.036	0.065
Thyroid	0.034	0.055
Urinary Bladder Wall	0.192	0.062
Uterus	0.057	0.066
Total Body	0.042	0.046
	rem/mCi	**rem/mCi**
Effective Dose Equivalent	0.101	0.065
Effective Dose	0.082	0.058

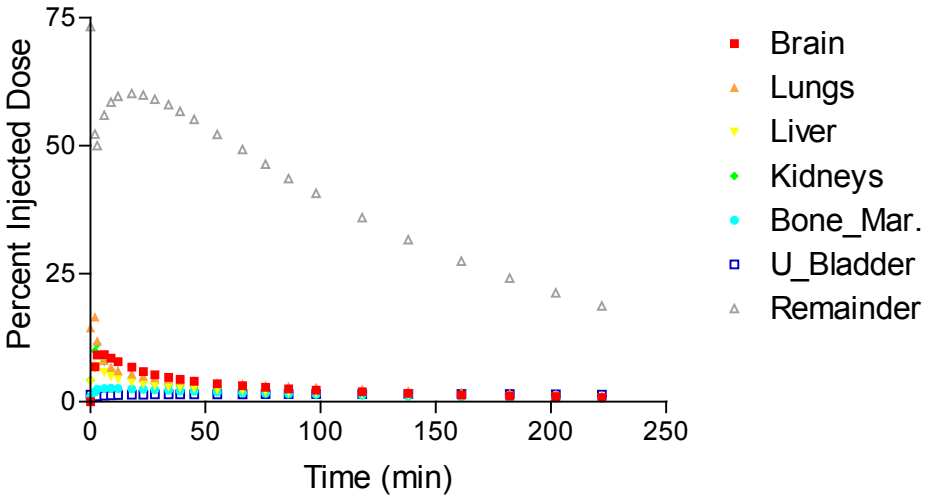

Figure 1. Time-activities curves for [^{18}F] FECNT as determined by PET imaging of six organs. Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

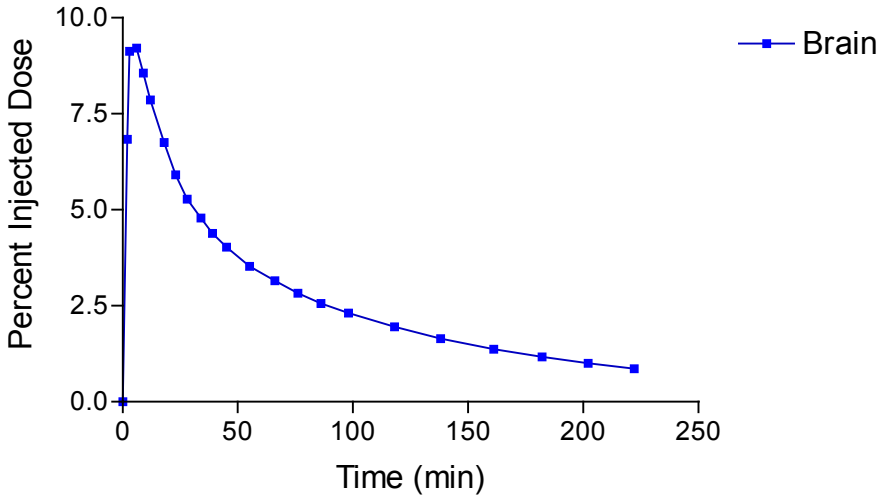

Figure 2. Time-activities curves for [18F] FECNT as determined by PET imaging of brain. Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

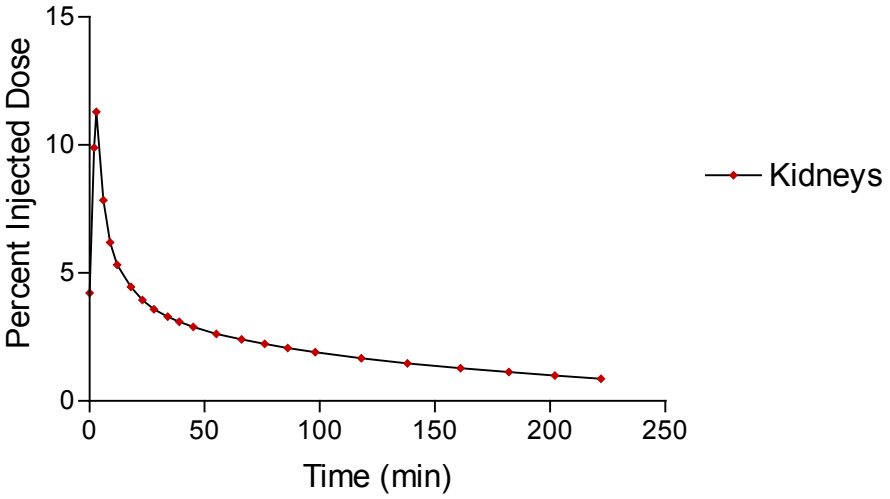

Figure 3. Time-activities curves for [18F] FECNT as determined by PET imaging of kidneys.Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

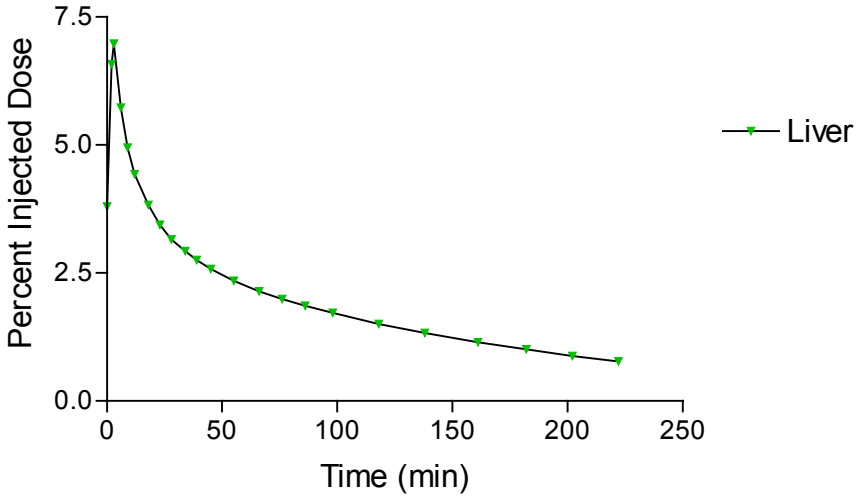

Figure 4. Time-activities curves for [^{18}F] FECNT as determined by PET imaging of liver. Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

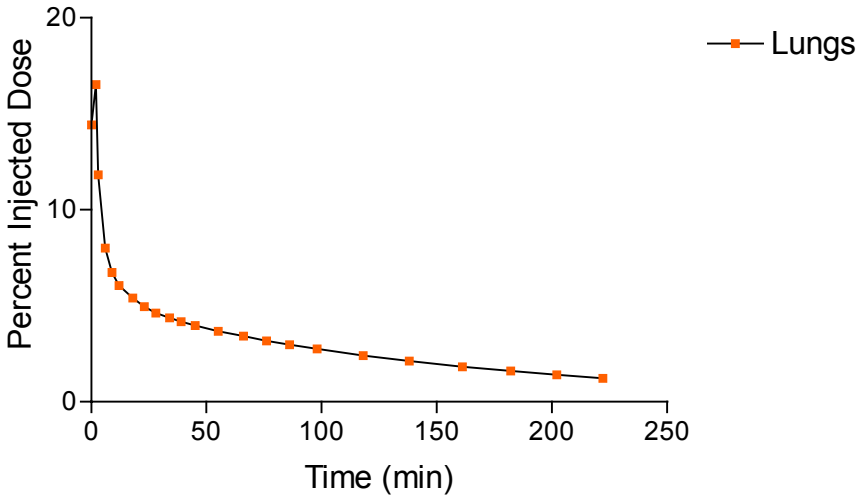

Figure 5. Time-activities curves for [18F] FECNT as determined by PET imaging of lungs.Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

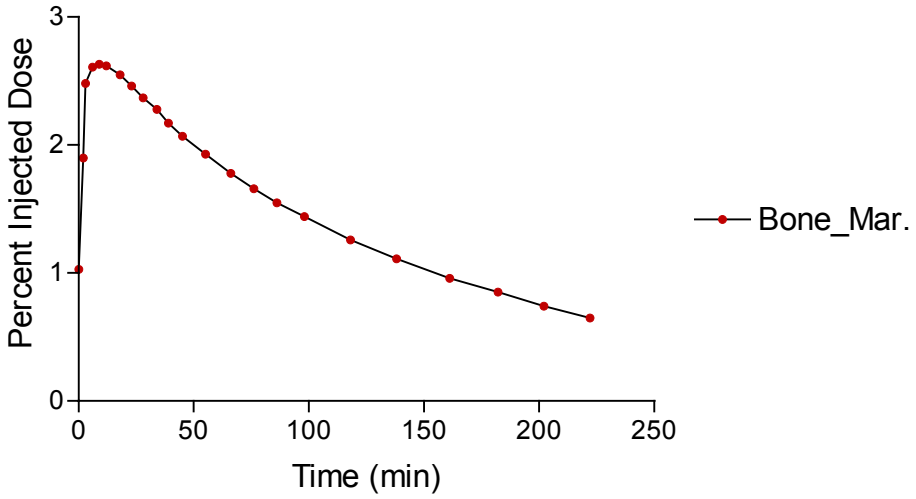

Figure 6. Time-activities curves for [18F] FECNT as determined by PET imaging of red bone marrow.Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

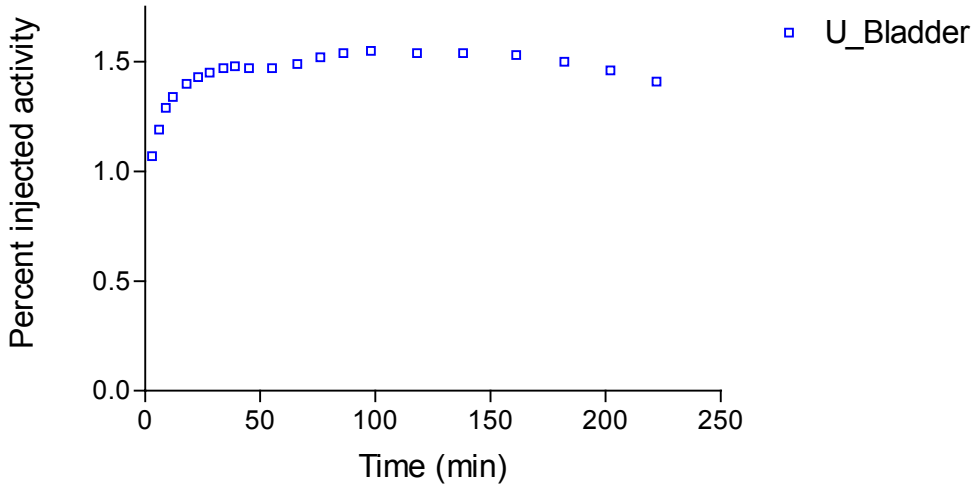

Figure 7. Time-activities curves for [18F] FECNT as determined by PET imaging of urinary bladder.Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.

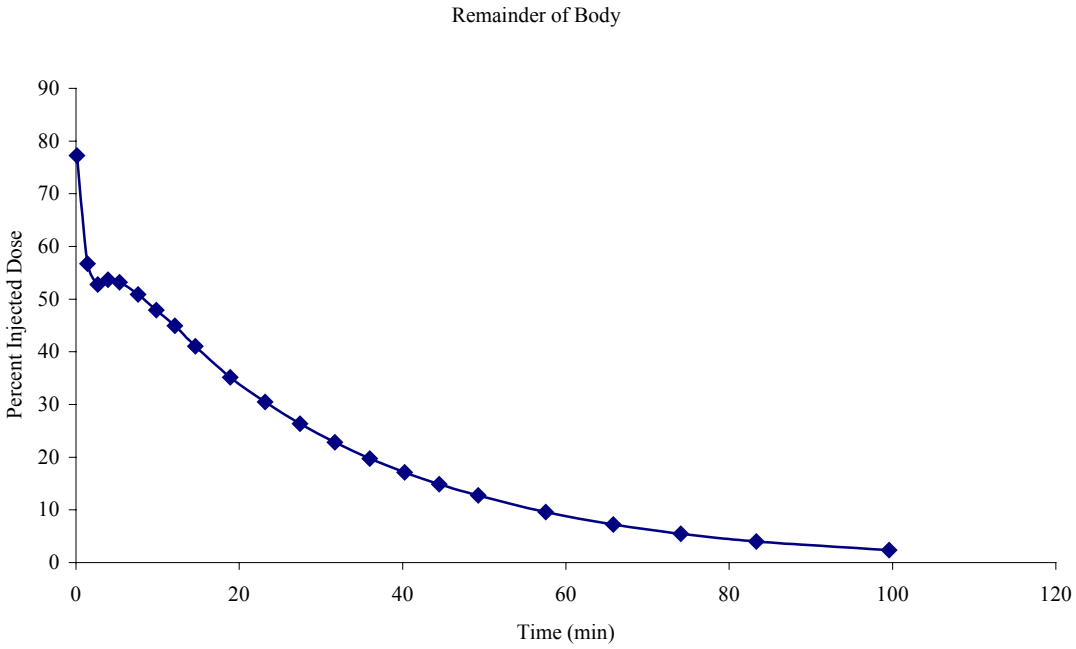

Figure 8. Time-activities curves for [18F] FECNT as determined by PET imaging. Data are expressed as the average for two monkeys and are non-corrected for radioactive decay.