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RESEARCH ARTICLE

Biodistribution and Radiation Dosimetry of the Serotonin 5-HT$_6$ Ligand [^{11}C]GSK215083 Determined from Human Whole-Body PET

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Abstract

Purpose: We measured the whole-body distribution of IV-injected [^{11}C]GSK215083, a new 5-HT$_6$ antagonist PET tracer, as a function of time in adult subjects, in order to determine the radiation exposure.

Procedures: After injection with a single bolus of [^{11}C]GSK215083 (range 330–367 MBq; mean 346 MBq), PET emission data were acquired for approximately 120 min in six subjects (three males and three females). Five organs were identified as exhibiting uptake above background. For these, regions of interest were delineated on emission images, and time–activity curves (TAC) generated. Residence times were calculated as the area under the curve of the TAC, normalized to injected activities and standard values of organ volumes. Dosimetry calculations were then performed using the computer program OLINDA/EXM 1.0.

Results: The mean effective dose averaged over both males and females (±standard deviation) was estimated to be 7.7±1.0 μSv/MBq (male 7.0±0.4; female 8.5±0.6). For the effective dose equivalent, the corresponding values are 7.8±1.2 μSv/MBq (male 6.8±0.5; female 8.9±0.1). The organ receiving the highest dose was the lung, with an average equivalent dose of 25.6±6.9 μSv/MBq (male 20.8±5.6; female 30.4±4.4).

Conclusion: The estimated radiation dose for [^{11}C]GSK215083 is consistent with those for other neuroreceptor ligands labeled with carbon-11. The somewhat higher dose estimate for females compared to males may reflect the difference in observed residence times and representative differences in the male and female phantoms used for dosimetry calculations. Based on conventionally accepted dose limits, [^{11}C]GSK215083 may be used for multiple PET scans in the same subject.

Key words: Biodistribution, Dosimetry, Positron emission tomography, [^{11}C]GSK215083, 5-HT$_6$ antagonist

Introduction

The 5-hydroxytryptamine 6 receptor (5-HT$_6$ R) is a comparatively recent addition to the serotonin receptor family, identified by two independent groups in 1993, using molecular cloning [1, 2]. 5-HT$_6$ R is a seven-transmembrane domain guanine nucleotide-binding protein (G protein)-coupled receptor, which is positively coupled to adenylate cyclase. The 5-HT$_6$ R is localized in the striatum, hippocampus, and cortex [1, 2] and is virtually absent outside the CNS, though 5-HT$_6$ messenger RNA has been found in the peripheral blood mononuclear cells of rhesus macaque monkeys [3] and the

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lymphoid tissue and lymphocytes of rats [4]. The physiological significance of these findings is unclear, and no reports of similar findings in humans are available.

The 5-HT$_6$ R activity modulates acetylcholinergic [5–8] and dopaminergic neurotransmission [8], and has been implicated in spatial learning and memory [9–11]. It has been proposed as a drug target for a number of neuropsychiatric conditions [12], with an increasing focus on the treatment of cognitive disorders [13].

^{11}C-GSK215083 [^{11}C-N-methyl]3-[(3-fluorophenyl)sulfonyl]-8-(4-methyl-1-piperazinyl) quinoline, is a selective positron emission tomography (PET) radioligand for the *in vivo* measurement of central 5-HT$_6$ R availability [14, 15]. The aim of this study was to collect whole-body human biodistribution data to estimate the radiation exposure following intravenous administration of [^{11}C]GSK215083.

Subjects and Methods

Subjects

The study population consisted of six healthy subjects (three males and three females, age 18–31; mean 25.5 years; SD 4.42). Suitability for participation including the absence of clinically significant illness or disease was assessed by interview, physical examination, electrocardiogram, vital signs measurements, routine blood tests, pregnancy test, and a drug and alcohol screen. This study was approved by the research ethics board for human subjects at the Centre for Addiction and Mental Health, Toronto, Canada.

Radiochemistry

[^{11}C]-methylation of the normethyl precursor SB 792988A (hydrochloride salt) with [^{11}C]-iodomethane was carried out inside an HPLC sample loop using our previously described "loop" method [16, 17]. The precursor (1.0 mg) was dissolved in a mixture of DMF (77 μl) and aqueous sodium bicarbonate (1 N, 7 μl), vortexed for 1 min and reacted on the loop for 1 min at RT with trapped [^{11}C]-CH3I. Following HPLC purification (Phenomenex LunaC18, 250×10 mm; 40/60 CH$_3$CN/H$_2$O + 0.1 N amm. formate, 8 ml/min), volatiles were removed under vacuum in a rotary evaporator at 70°C. Upon formulation in buffered saline, [^{11}C]-GSK215083 was obtained in 20–25% radiochemical yield (uncorrected for decay, from [^{11}C]-CO$_2$) in 24 min post end-of-bombardment.

PET/CT Scanning

Scans were performed using a Siemens-Biograph HiRez XVI PET camera system (Siemens Molecular Imaging, Knoxville, TN, USA), the performance characteristics of which have been described previously [18]. Following the acquisition of a scout view for accurate positioning, subjects underwent transmission CT (140 kVp, 30 mA, scan range 104 cm) After a single intravenous bolus injection of [^{11}C] GSK215083 (injected activity 330–367 MBq; mean 346; SD 15),

serial whole-body PET scans were acquired from head to midthigh for a period of up to 120 min, as a series of overlapping bed positions with a progressive increase of scan duration per bed position (positions 1 and 2, 15 s; 3 and 4, 30 s; 5 and 6, 60 s; 7, 120 s; 8, 180 s; 9, 240 s). Each subject underwent nine whole-body PET acquisitions with eight or nine bed positions per whole-body acquisition depending upon their height (two subjects having nine bed positions per scan), resulting in an acquisition duration of 510 or 750 s per whole-body scan. Subjects remained in position on the scanning bed for the duration of the scanning period. The difference between the time in the scanner and the duration of image acquisition is due to the time required to move between bed positions and the time between the end of one wholebody acquisition and the start of the next.

Data were normalized, gap filled, dead time corrected, arc corrected (both radial and axial), and converted from 3D to 2D using FORE [19] prior to reconstruction using the direct inverse Fourier transform algorithm [20]. A Gaussian filter was applied postreconstruction with an 'FWHM' of 5 mm in the x, y, and z directions. The attenuation correction was derived from a CT-derived mu-map, and the 3D scatter correction was model based [21].

Regions of Interest

Summed images (0–120 min) were visually inspected, tissues exhibiting uptake above background uptake were identified, and regions of interest (ROIs) were delineated on corresponding emission images. ROIs were drawn manually on these organs using Analyze software (Mayo Clinic) to obtain the mean activity concentration in each region and each pass (within subject, the same ROIs were applied to data from all passes). Included organs were the brain, heart, liver, lung, and stomach. For each subject summed images for different time ranges were used to draw the ROIs depending on the observed uptake in the different organs. For regions with low uptake, such as the lung early add images were used in conjunction with the CT to guide the definition of the ROI. The location of all organs was verified using the CT image. Finally the position of each ROI in each subject was visually inspected for all frames to ensure that the ROI was in the corresponding organ

Residence Time and Absorbed Dose Calculations

Mean residence times (MRTs) for each organ were calculated as follows (Eq. 1):

$$\mathrm{MRT} = \left(\mathrm{AUC} \times V_{\mathrm{organ}}\right)/\text{injected activity} \qquad (1)$$

where AUC is the area under the curve of the nondecay corrected time–activity curve (TAC) and V_{organ} is the tabulated organ volume as used in the OLINDA/EXM® version 1.0 [22].

Depending on the shape of the TAC, two cases were distinguished (see Fig. 2): for monotonically decaying TACs (e.g., lungs and heart), a two exponential model $\left(\mathrm{TAC} = A_1 e^{-t\beta1} + A_2 e^{-t\beta2}\right)$ was fitted to the TAC and the resulting parameters were used to analytically calculate the AUC $\left(\mathrm{AUC} = A_1/\beta_1 + A_2/\beta_2\right)$. For nonmonotonic TACs the AUC was calculated using trapezoidal integration over the duration of the TAC plus a term that represents solely radioactive decay starting from the last point in the TAC.

Table 1. Subject data and injection parameters for [^{11}C]GSK215083

	Subject ID	Sex	Age (year)	Weight (kg)	Injected activity (MBq)	Mass injected (μg)
	S001	M	28	90	339	4.2
	S006	M	24	86.3	330	3.9
	S008	M	31	81.8	332	3.9
	S003	F	27	65.9	353	3.0
	S009	F	18	77.2	356	3.7
	S018	F	25	78	367	5.3
Mean	N/A	N/A	25.50	79.87	346	4.0
SD	N/A	N/A	4.42	8.41	15	0.8
Min	N/A	N/A	18	65.9	330	3.0
Max	N/A	N/A	31	90	367	5.3

The residence time of the remainder (assumed to be homogeneously distributed in the body) was obtained by subtracting the sum of all defined organ residence times from the inverse of the decay constant for ^{11}C. MRTs for the organs mentioned above were entered into the dose estimation software OLINDA|EXM® version 1.0 [22] to calculate the radiation dose to individual organs, and resulting effective dose equivalents and effective doses (ED).

Since ICRP 103 tissue-weighting factors (W_T) are not implemented in OLINDA/EXM 1.0, the male and female EDs are based on W_T from ICRP-60. Extraction of organ dose data from OLINDA/EXM 1.0 and application of W_T from ICRP 103 are possible but not straightforward as phantoms used in OLINDA/EXM 1.0 lack some of the organs used in the ICRP 103 scheme.

Results

Subject demographic data and ^{11}C-GSK215083 injection parameters are given in Table 1. Whole-body PET images from a representative subject are displayed in Fig. 1, and
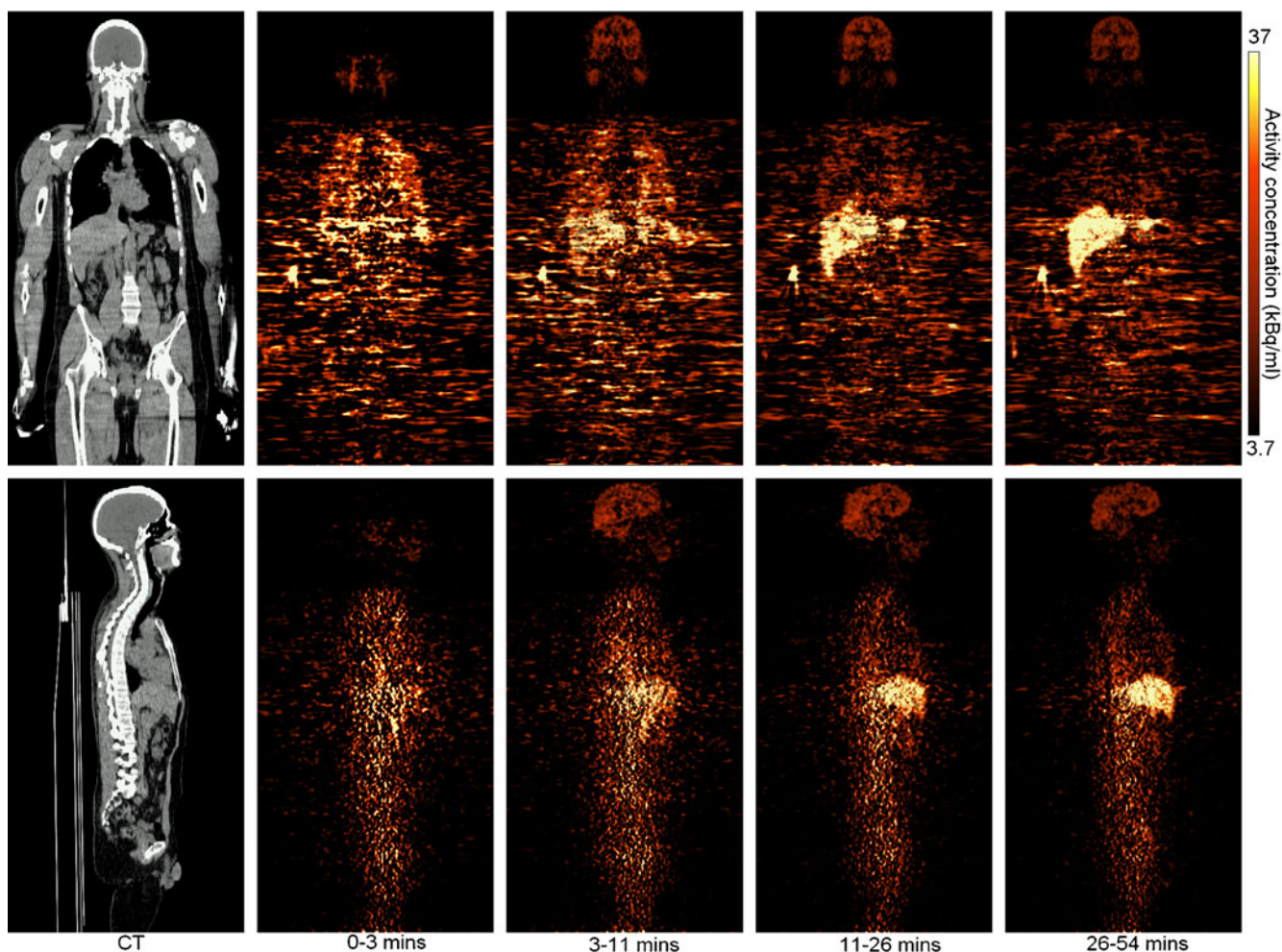

Fig. 1. Coronal (*top row*) and sagittal (*bottom row*) slices of whole-body images in a representative subject; *numbers* minutes post-tracer injection for each set of decay corrected integral PET images.
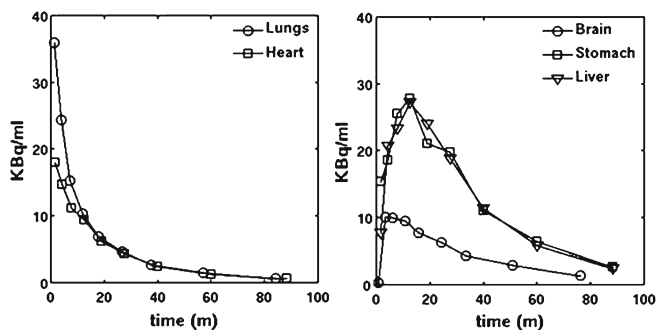
Fig. 2. Time–activity curves for measured organs, data from a representative subject.

time activity curves in Fig. 2. Mean residence times are displayed in Table 2. Organ absorbed doses, effective dose equivalent, and effective dose are displayed in Table 3. In all subjects, the heart and lung decreased monotonically, whereas the brain, stomach, and liver were unimodal, reaching peak values approximately 3, 15, and 20 min after injection.

The mean effective dose averaged over both males and females (±standard deviation) was estimated to be 7.7± 1.0 μSv/MBq (male 7.0±0.4; female 8.5±0.6). For the effective dose equivalent, the corresponding value is 7.8± 1.2 μSv/MBq (male 6.8±0.5; female 8.9±0.1).

Discussion

We estimated the radiation dosimetry of ^{11}C-GSK215083 from data acquired with whole-body PET in six human subjects. The observed biodistribution most likely reflects rapid distribution in the intravascular compartment, followed by pulmonary uptake and disposition in tissues according to their blood perfusion rate and affinity for the tracer; data suggest distribution to the liver followed by excretion via the GI tract.

The estimated radiation doses are consistent with those for other neuroreceptor ligands labeled with carbon-11 [23]. The somewhat higher doses in females compared to males reflect the difference in observed residence times and representative differences in the male and female phantoms used for dosimetry calculations.

Restrictions on radiation exposures differ from country to country, though most are based on the recommendations of

Table 3. Mean organ dose estimates (in microsieverts per megabecquerel, organ doses are expressed as equivalent doses)

Organ	Male (n=3)	Female (n=3)
Adrenals	3.5	4.4
Brain	5.6	8.8
Breasts	2.2	2.6
Gallbladder wall	4.2	5.3
LLI wall	2.0	2.2
Small intestine	2.5	2.5
Stomach wall	18.2	15.9
ULI wall	2.5	2.9
Heart wall	4.8	6.0
Kidneys	2.7	3.3
Liver	17.2	27.4
Lungs[a]	20.8	30.4
Muscle	2.1	2.4
Ovaries	2.2	2.3
Pancreas	3.4	4.3
Red marrow	2.1	2.4
Osteogenic cells	2.9	3.5
Skin	1.6	1.9
Spleen	2.5	3.0
Testes	1.7	N/A
Thymus	2.6	3.0
Thyroid	2.0	2.7
Urinary bladder wall	2.0	2.1
Uterus[b]	2.2	2.0
Total body	2.9	2.8
Effective dose equivalent	6.8±0.5	8.9±0.1
Effective dose	7.0±0.4	8.5±0.6

Values are mean±standard deviation
[a]Critical organ
[b]Included in male phantom

the ICRP [24, 25]. European Union member states have adopted the guidance in ICRP Publication 62 [26]. Following the World Health Organization categorisation of risk levels, effective dose constraints no greater than 10 mSv per study are recommended where research subjects do not receive a direct benefit from participation. As a result dose constraints implemented for PET research studies in healthy volunteers are typically somewhat lower than ICRP-recommended occupational effective dose limits (20 mSv per year, averaged over 5 years, not exceeding 50 mSv in a single year).

For studies performed in the USA, the maximum allowable single dose to the whole-body, blood-forming organs, lens of the eye, or gonads is 30 mSv, with a maximum annual dose of 50 mSv. The maximum allowable single and annual doses to all other *organs* are 50 and 150 mSv, respectively [27]. In the case of ^{11}C GSK215083,

Table 2. Mean residence times in hours of [^{11}C]GSK215083 for five measured organs and remainder of body

Organ	Male (n=3)	Female (n=3)
Brain	0.023±0.006	0.032±0.002
Lungs	0.078±0.022	0.090±0.014
Heart	0.005±0.001	0.005±0.002
Liver	0.097±0.022	0.118±0.111
Stomach	0.009±0.001	0.008±0.003
Remainder	0.278±0.027	0.237±0.018

Values are mean±standard deviation

Table 4. US Injected activity limits (in megabecquerels) arising from the dose to the lung

	Male	Female
Single study	2,404	1,643
Cumulative annual	7,143[a]	5,882

Reference [27]
[a]The annual whole-body ED limit of 50 mSv would be exceeded before the lung became dose limiting

the lung is the organ with the highest equivalent dose (the "critical organ"); for a single study, the lung is dose limiting, in that the RDRC organ limit of 50 mSv would be reached before the whole-body limit of 30 mSv. For cumulative exposures, in males the maximum annual injected activity is driven by the whole-body limit of 50 mSv; whereas in females who have a slightly higher lung exposure, the lung remains dose limiting, in that the 150-mSv organ dose limit would be exceeded before the 50-mSv whole-body limit (Table 4).

When planning studies using PET–CT exposure from CT scanning should be considered. In this study subjects were scanned from the from the top of the head to the midthigh for the purpose of anatomical localisation and attenuation correction; the resulting exposure from the CT was estimated at 5.1 mSv, in a typical PET study involving a single head CT for attenuation correction exposure would be in the region of 0.2 mSv (depending on the scanner and protocol used). Recent work suggests that injected doses of ca. 370 MBq of [^{11}C]GSK215083 (ED 2.8 mSv) will be sufficient to quantify central 5-HT$_6$ receptors (Parker C., *submitted*). In conclusion [^{11}C] GSK215083 may be used in multiple PET scans in the same subject within conventionally accepted dose limits, facilitating its use in receptor occupancy studies to support drug development.

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