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Radiation dosimetry of *N*-([¹¹C]methyl)benperidol as determined by whole-body PET imaging of primates

Jo Ann V. Antenor-Dorsey,

Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Richard Laforest,

Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA

Stephen M. Moerlein,

Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA

Tom O. Videen, and

Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA.

Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

Joel S. Perlmutter

Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA. Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA. Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA. Program in Physical Therapy, Washington University School of Medicine, St. Louis, MO, USA

Joel S. Perlmutter: joel@npg.wustl.edu

Abstract

Purpose—*N*-([¹¹C]methyl)benperidol ([¹¹C]NMB) can be used for positron emission tomography (PET) measurements of D₂-like dopamine receptor binding in vivo. We report the absorbed radiation dosimetry of i.v.-administered [¹¹C]NMB, a critical step before applying this radioligand to imaging studies in humans.

Materials and methods—Whole-body PET imaging with a CTI/Siemens ECAT 953B scanner was done in a male and a female baboon. After i.v. injection of 444–1221 MBq of [¹¹C]NMB, sequential images taken from the head to the pelvis were collected for 3 h. Volumes of interest (VOIs) were identified that entirely encompassed small organs (whole brain, striatum, eyes, and myocardium). Large organs (liver, lungs, kidneys, lower large intestine, and urinary bladder) were sampled by drawing representative regions within the organ volume. Time–activity curves for each VOI were extracted from the PET, and organ residence times were calculated by analytical integration of a multi-exponential fit of the time–activity curves. Human radiation doses were estimated using OLINDA/EXM 1.0 and the standard human model.

Results—Highest retention was observed in the blood and liver, each with total residence times of 1.5 min. The highest absorbed radiation doses were to the heart (10.5 mGy/kBq) and kidney (9.19 mGy/kBq), making these the critical organs for [¹¹C]NMB. A heart absorption of 50 mGy would result from an injected dose of 4,762 MBq [¹¹C]NMB.

Correspondence to: Joel S. Perlmutter, joel@npg.wustl.edu.

Present address: J. S. Perlmutter, Campus Box 8225, 4525 Scott Avenue, St. Louis, MO 63110, USA

Conclusions—Thus, this study suggests that up to 4,762 MBq of [^{11}C]NMB can be safely administered to human subjects for PET studies. Total body dose and effective dose for [^{11}C]NMB are 2.82 mGy/kBq and 3.7 mSv/kBq, respectively.

Keywords

[^{11}C]NMB; Radiation dosimetry; D₂-like receptor; Radioligand

Introduction

In vivo measurements of dopaminergic D₂-like receptor binding may provide important insights into the pathophysiology and treatment of a variety of neuropsychiatric disorders including Parkinson's disease [1], dystonia [2], Tourette's syndrome [3], and schizophrenia [4]. [^{11}C]Raclopride has been used as a dopaminergic D₂-like receptor binding radioligand due to its greater selectivity compared to radiolabeled butyrophenone analogs [5–7]. [^{11}C]Raclopride, however, is susceptible to displacement by endogenous dopamine [8,9], providing a strategy for measuring release of endogenous dopamine but confounding interpretation of positron emission tomography (PET)-based measurements of D₂-like receptors. [^{123}I]Epidepride and [^{18}F]fallypride have relatively higher affinity for D₂-like-specific binding sites than [^{11}C]raclopride but remain susceptible to displacement by endogenous dopamine [10]. [^{18}F](*N*-methyl)benperidol ([^{18}F]NMB) exhibits greater D₂-like receptor selectivity compared to radiolabeled spiperone and its analogs [6–8], and unlike [^{11}C]raclopride [9,10], [^{123}I]epidepride, and [^{18}F]fallypride, [^{18}F]NMB resists displacement from specific binding sites by endogenous dopamine [2].

The relatively long half-life of [^{18}F] (110 min) increases radiation exposure and limits the administered dose of [^{18}F] NMB. Synthesis of the ligand as *N*-([^{11}C]methyl)benperidol ([^{11}C]NMB) could provide the same D₂-like selectivity of the radioligand but with a shorter 20-min half-life. This shorter half-life potentially permits administration of larger doses of the radioligand, improving counting statistics, yet reducing radiation exposure. The goal of our study is to measure the absorbed radiation exposure after intravenous administration of [^{11}C]NMB. We have chosen to use nonhuman primates, as the metabolism and physiology of these animals are closer to humans than rodents, making extrapolation to humans more reasonable.

Materials and methods

Radiopharmaceutical preparation

N-([^{11}C]Methyl)benperidol was synthesized as previously reported [11] via *N*-methylation of benperidol (Janssen Research Products, Flanders, NJ, USA) using [^{11}C]methyl iodide. Carbon-11 was prepared as $^{11}\text{CO}_2$ using the Washington University JSW BC 16/8 cyclotron and the $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ nuclear reaction. The $^{11}\text{CO}_2$ was converted to $^{11}\text{CH}_3\text{I}$ using the microprocessor-controlled PETtrace MeI MicroLab (GE Medical Systems, Milwaukee, WI, USA) and immediately used to [^{11}C]methylate benperidol. Product [^{11}C]NMB was purified via semipreparative high-performance liquid chromatography (HPLC) and reformulated in a 10% ethanol/normal saline solution. The radiochemical purity exceeded 95%, and the specific activity exceeded 1,000 Ci/mmol, as determined by analytical HPLC.

Instrumentation

PET images were acquired using a ECAT 953B scanner (Siemens/CTI, Knoxville, TN) in stationary 2D mode [12,13]. Single scans have 31 slices with 3.37 mm separation for an axial field of view of 10.5 cm. Scans were reconstructed with measured attenuation and

scatter correction [14] using a ramp filter to produce images with transverse resolution of 5.7 mm and axial resolution of 4.2 mm full-width at half-maximum at slice centers. PET image counts were calibrated to both a well counter and a dose calibrator to convert measured PET uptake to microcuries of ^{11}C .

Subjects

One male (23 kg) and one female (12.8 kg) *Papio anubis* baboons were used in these studies. All experimental procedures were approved by the Animal Studies Committee of Washington University in St. Louis.

The baboons were fasted overnight before each study. Each animal was initially anesthetized with ketamine 10–15 mg/kg i.m.; a 20-gauge plastic catheter was inserted into a limb vein to permit radiotracer; another 20-gauge plastic catheter was inserted into a femoral artery for arterial blood sampling; and a soft-cuffed endotracheal tube was inserted into the trachea to permit ventilation with isoflurane to maintain anesthesia. Lacrilube was placed into the animal's eyes to protect the corneas. Pulse, end-tidal PCO_2 and rectal temperature were monitored.

Data acquisition

Before injection of the radioligand, 15-min transmission scans were collected in four different positions for attenuation correction measurements. These positions corresponded precisely with the alignment for the 32 subsequent emission scans collected after intravenous injection of $[^{11}\text{C}] \text{NMB}$. The animal was firmly secured to the scanning table, allowing us to move the animal to a set position for each of the four assigned body sections. The assigned sections (and tissues included therein) were: A (eyes and whole brain, including striatum), B (heart and lungs), C (liver and kidneys), and D (urinary bladder and lower large intestines).

Immediately after acquisition of the transmission scans, 444–1221 MBq of $[^{11}\text{C}] \text{NMB}$ was injected i.v. over 30 s into an antecubital vein. Sequential scans and arterial blood samples were obtained for each baboon over a total scanning time of approximately 3 h. Eight successive PET scans were done for each of the four tomographic sections, with acquisition times of 60, 120×2, 180, 300×3, and 600 s (Fig. 1). At least thirty 0.5 ml arterial blood samples were collected, initially at 10-s intervals for the first 3 min, then at 1-min intervals for the next 15 min, and finally at 30-min intervals for the last 2 h. Most of the samples were taken in the first 3 min to ensure adequate description of the arterial input of radioactivity. Total radioactivity content in each blood sample was measured in a well counter cross-calibrated with the PET scanner. Arterial blood sampling was done once in each of the two baboons.

Image quantification

Radioactivity from the blood compartment localized primarily within nine organs. All organs that contained a visible accumulation of activity were included for image quantification.

Image quantification involved two approaches, depending upon the size of the organ under consideration. For small organs (whole brain, striata, eyes, and heart), volumes of interest (VOIs) widely encompassing entirely the target organ were drawn to ensure that the entire accumulated radioactivity was included. The volume of each VOI was determined by multiplying the number of voxels encompassed by the VOI times the voxel dimensions ($2.0 \times 2.0 \times 3.375$ mm). The PET regions chosen for the two striata enclosed 14.6–32.1 cc for both sides of the brain, or about 12 times the true size of the striata, ensuring that our data

analysis method included most of the radioactivity from the striata in the corresponding VOIs. The same procedure was done for defining the VOIs representing the heart and the eyes. The total volume of the eye VOIs amounted to 17.4–38.3 cc, which is more than thrice the volume of a pair of typical baboon eyes [15]. The volumes of the VOIs that correspond to the four organs in which VOIs encompassed the entire organ are listed in Table 1.

To obtain regional radioactivity measurements, the position of each VOI was held constant for all sequential scans made on an animal. As organs were sampled on multiple PET slices, radioactivity levels from all of the corresponding VOIs for a given organ were summed to obtain the entire radioactivity accumulation in that organ. The PET-based total regional radioactivity measurements were then used to determine the percent injected dose per organ (%ID/organ).

For larger organs (lungs, liver, kidney, and urinary bladder), we could not visualize a region encompassing more than the entire organ on the emission or transmission images, making it difficult to confidently measure the radioactivity uptake of the entire organ. For this reason, several small VOIs were chosen to include all areas of selective radioactivity accumulation within the target organ. Then, the average radioactivity concentrations across all of the regions for a specific organ were averaged and multiplied by the entire organ weight to give a liberal estimate of the radioactivity accumulation within the total organ. Organ weights were based on standard organ and tissue volumes [16,17]. This approach overestimates the organ dose as it assumes that regions of nonselective accumulation within an organ have the same uptake of radioactivity as those regions with selective accumulation.

No loss of urine or fecal matter was observed in these animals during each of these studies. Thus, corrections to the absorbed dose calculations for radioactivity loss through these routes were not needed.

Time–activity curves

Time–activity curves were constructed for the various organs using the mean PET counts in each organ VOI converted to kBq per cc. The blood content within the organs was included in each organ, producing a more accurate assessment of the dose delivered to the organ by the penetrating and nonpenetrating radiation. The standard organ volumes were normalized to each animal's weight. The %ID for each measured organ for the four studies was averaged together to yield a combined time–activity curve for each sampled organ.

In calculating the time–activity curves, the midpoint of each scan was recorded as the time elapsed since the start of radioligand injection. Data for the different organs were fitted by a least-square regression to achieve a maximum correlation. The fitted function was composed of combinations of exponential functions that represent the uptake and washout phases of the tracer's kinetics.

Residence-time calculations

Residence times for each organ were obtained by analytical integration of the time–activity curves. Each least-square fit was integrated from 0 to ∞ after initially multiplying by the physical decay of ^{11}C . The fit excluded physical decay of the radionuclide so that biological trends would be more clearly evident. Physical decay was then included in determining residence times. The residence times for the spleen and red marrow were calculated from the blood residence time. For the spleen, the residence time was calculated from the blood fraction of the spleen which is 1.5% of its volume [18]. For the red marrow, the marrow residence time is taken from $A_{\text{rm}} = 0.19/(1 - 0.39)A_{\text{Blood}}$ [18,19].

Residence times for 12 source organs (Table 2) were derived from the time–activity data of the nine image regions. The value for blood was measured from successive arterial blood samples. These samples were weighed and radioactivity measured in a NaI(Tl) well counter. Even though no obvious tracer accumulation was evident in the hematopoietic organs (spleen, red marrow), they were assigned residence times based on their blood volume. The residence time assigned to the remainder-of-body comprised blood activity that was not specifically assigned to an organ and any “missing” activity not accounted for in the sampled organs.

Organ-absorbed dose

The mean dose-to-target organ per unit administered activity was calculated with the program OLINDA/EXM 1.0 software package [20] using the standard human male model and the residence times calculated above. Organ dose estimates were conservative, as they included irradiation from activity in the blood volume of each organ. This is similar to the way in which the contents of excretory organs (intestines, kidneys) are included in the calculation of the absorbed dose of these organs.

The OLINDA/EXM head model for the human adult was used in conjunction with the sphere model to calculate the radiation dose estimate to the eyes, as the eyes are not a target organ in the standard MIRD scheme. The sphere model in OLINDA/EXM permits calculation of the self-dose to a spherical organ of various sizes containing a uniform distribution of radioactivity. The sphere calculations were performed using a sphere size of 6.2 cc and the observed residence time. Because the radioisotope of this tracer is ^{11}C , most of the radiation deposition comes from the positron kinetic energy before annihilation and, to a lesser extent, from the 511-keV annihilation photons.

Results

Radioactivity distribution

Table 2 gives the distribution of radioactivity in the nine primary organs for tracer location as determined from inspection of PET images at approximately 1 and 2 h after i.v. injection of [^{11}C]NMB. Our studies on [^{18}F]NMB indicate that D_2 -like receptor-specific localization in brain of the radioligand is high within this time interval [21]. Data are reported in terms of percent injected dose per organ and corresponding standard errors.

Note that radioactivity accumulates substantially within the liver and kidney, whereas accumulation of activity within the urinary bladder is low. In addition, clearance from the lungs reflects clearance of the radioligand from the blood compartment.

Time–activity curves

Representative time–activity curves are shown in Fig. 2. Curves are illustrated for whole brain, striatum, blood, liver, heart, and kidneys. The total blood–activity curve was measured from arterial blood samples collected during the scan. Also shown is the time course of radioactivity in the remainder of the body. This curve consisted of activity in blood not specifically assigned to an organ and any “missing” activity. “Missing” activity represents nonselective distribution of activity throughout the body. For each set of curves, the scatter plots were fitted with mono- or bi-exponential functions by least square minimization (Fig. 2).

Residence times

The residence time τ was obtained by analytical integration of the least-squares fit of the time–activity curves from 0 to ∞ after including the physical decay of the radioisotope.

Table 3 gives the mean value of the residence times of the tracer in 12 organs over all four experiments, with corresponding SE. The error is representative of the between-scan variability and not the uncertainty of the fit. Residence times for the spleen and red marrow were estimated by multiplying the blood concentration by the appropriate organ/compartmental blood volumes [16,17].

Organ-absorbed dose

Results of the OLINDA/EXM 1.0 dose calculations for the PET studies of [^{11}C]NMB are given in Table 4. These individual dose estimates include not only the component attributed to organ self-irradiation, but also that fraction attributable to external irradiation from source organs in close proximity. The relative contribution of source organs to the absorbed dose for a given tissue is determined by their respective S values. The data are presented as the mean $\pm$ SE and are reported in units of mGy/kBq. The expressed error represents the observed inter-animal variability of radiotracer uptake. The number of organs tabulated in Table 4 is larger than that of Tables 2 and 3, as an organ does not have to contain appreciable radioactivity itself to endure a radiation burden arising from radiation localized in nearby tissues.

The heart and the kidney received the highest doses followed by the lower and upper large intestines and the liver. None of the organs receive a radiation burden exceeding 10.5 mGy/kBq. The dose to the eyes was evaluated from the OLINDA/EXM Head and Spheres model. The radiation dose to the eyes from the brain only was 0.24 mGy/kBq, while the self-dose to the eyes as calculated by the sphere model was 11.36 mGy/kBq. The latter value is similar to the highest organ dose.

Discussion

An important step in the transition of a positron-emitting radiochemical into a clinically useful PET radiopharmaceutical is the accurate assessment of the absorbed dosimetry associated with its use. In this work, we extrapolate human dosimetry from PET-based measurements of radioactivity after i.v. administration of [^{11}C]NMB in baboons. These animals are genetically closer to humans than other animals currently used for radiation dosimetry studies, thereby providing a closer model of human metabolism and physiology. The tissue biodistribution of [^{11}C]NMB is characterized by relatively rapid blood clearance of the tracer and some hepatic metabolism. The organ distribution of radioactivity (Table 2) and the associated residence times for the various organs (Table 3) reflect the *in vivo* hepatic degradation of [^{11}C]NMB to radiometabolites that subsequently empty into the intestinal tract. Hepatic metabolism is common to butyrophene D_2 antagonists [22].

The heart is one of the main critical organs for [^{11}C] NMB. This cardiac exposure is likely due to a combination of selective uptake with the location of dopamine receptors in the heart [23], and the high blood volume in the heart that contains substantial radioactivity at early times after injection of [^{11}C]NMB. Another radiolabeled butyrophene with selectivity for D_2 receptors, I-2'-iodospiperone (2'-ISP), also has high myocardial accumulation of radioactivity [24] as measured by single photon emission tomography. Although the brain also contains D_2 receptors in high concentration, especially in the striatum, administration of [^{11}C]NMB yields only a low absorbed dose of approximately 3.04 mGy/kBq to the brain due to the modest partitioning of the compound into brain.

The radiation dose each organ received was conservatively estimated (i.e., errors biased to overestimates) in our calculations. For radioactivity concentrations, the areas of highest radioactivity concentrations in an organ were used as representative of the entire organ mass. Thus, the actual concentration and associated radiation burden of these organs are

likely to be substantially lower. Nevertheless, for a maximum absorbed dose of 50 mGy to the critical organ (as required by the U.S. Food and Drug Administration for institutional Radioactive Drug Research Committee approval), our estimates indicate that 50 mGy/(10.5 mGy/kBq)=4,762 MBq of [^{11}C]NMB can be administered to human subjects, compared to the allowed dose of 314.5 MBq for [^{18}F]NMB [25]. Thus, it is apparent that the radiation burden arising from [^{11}C]NMB is substantially lower than that of [^{18}F]NMB, despite the identical chemical structures of the two radiotracers. Part of this difference is attributable to the shorter physical half-life of carbon-11 in the title compound. However, it should also be noted that the molecular location of the radiolabels differs for the two radioligands, which leads to the generation of different radiometabolites with distinct patterns of distribution and excretion.

In fact, the critical organs for [^{11}C]NMB dosimetry are the heart, kidneys, lower large intestines, and liver, whereas the critical organs for [^{18}F]NMB were the lower large intestines, gallbladder, and liver (absorbed radiation doses 159, 76, 57 mGy/kBq, respectively; [25]). In [^{11}C]NMB, the carbon-11 is situated on the amide nitrogen of the benzimidazolinone group, whereas for [^{18}F]NMB, the fluorine-18 is located at the other end of the molecule, on the *p*-fluorobenzoyl moiety. Thus, [^{18}F]NMB is probably metabolized to *para*-[^{18}F]fluorobenzoylpropionic acid [22] and excreted through hepatic pathways, while the biotransformation of [^{11}C]NMB involves alternative excretion pathways with lower dosimetry burden to the liver, gall bladder, and intestines. In this way, divergent organ localization of the respective radiometabolites also contributes to differences in the absorbed radiation dose derived from [^{11}C]NMB and from [^{18}F]NMB.

Conclusions

We have determined the absorbed radiation dosimetry associated with i.v. injections of [^{11}C]NMB by whole-body PET imaging of primates and OLINDA calculation methods. The critical organs were the heart (10.5 mGy/kBq) and kidneys (9.19 mGy/kBq). The results confirm the utility of whole-body PET imaging in preclinical evaluations of radiopharmaceutical dosimetry, and this study proposes that up to 4,762 MBq of [^{11}C]NMB can be safely administered to human subjects for PET measurements of D₂-like receptor binding.

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Fig. 1.
Outline of the scanning sequences for the four studies: ■ transmission scan; ■ emission scan

Fig. 2. Time-activity curves for $[^{11}\text{C}]$ -NMB as determined by PET imaging of six compartments: **a** striatum, **b** brain, **c** heart, **d** liver, **e** kidney, **f** blood, and **g** remainder of the body. *Errors bars* represent the uncertainty in the average values due to *between-scan* fluctuations. The *solid line* represents the result of the multi-exponential fit and the *dashed line* represent this fit accounting for the decay of ^{11}C

Table 1

Voxels of interest (VOI) used for image quantification

Voxels	Organ VOI volume (cc)	Total sampled volume (cc)
VOIs that encompass the organ		
Striatum	14.7–32.1	
Whole brain	164.5–227.0	
Heart	76.2–191.6	
Eyes	17.4–38.3	
VOIs that sample the organ		
Lungs		12.7–18.4
Liver		22.1–32.1
Kidneys		46.8–52.7
Lower large intestines		4.8–11.8
Bladder		5.31–17.2

Table 2Approximate biodistribution of radioactivity after i.v. injection of [^{11}C]NMB

Organ	Percent injected dose per organ (%)			
	Scan time (0.95±0.17 h)		Scan time (1.85±0.18 h)	
	Average	SD	Average	SD
Striatum	0.266	0.026	0.184	0.016
Whole brain	1.59	0.29	1.06	0.20
Eyes	0.13	0.08	0.105	0.051
Heart	1.15	0.29	0.72	0.16
Lungs	0.47	0.097	0.34	0.07
Kidney	1.20	0.59	1.12	0.46
Liver	4.64	2.14	6.33	4.34
Lower large intestines	0.96	0.25	0.57	0.07
Bladder	0.096	0.020	0.071	0.019

Table 3Residence times of [^{11}C]NMB in selected organs

Organ or tissue	τ (s)
Lower large intestines	25.1 $\pm$ 3.8
Upper large intestines	25.1 $\pm$ 3.8
Kidney	31.8 $\pm$ 9.1
Liver	90.0 $\pm$ 30.9
Lung	17.4 $\pm$ 4.6
Striatum	5.77 $\pm$ 1.23
Brain	41.1 $\pm$ 8.40
Eyes	2.06 $\pm$ 0.06
Heart	37.3 $\pm$ 1.1
Marrow	6.4 $\pm$ 0.6
Spleen	4.5 $\pm$ 0.5
Blood	91.0 $\pm$ 9.0

Table 4Absorbed dose estimates from [^{11}C]NMB based on whole-body imaging of primates

Target organ	Dose estimate (mGy/kBq)
Adrenals	3.13±0.22
Brain	3.04±0.62
Breasts	2.24±0.21
Gallbladder wall	3.41±0.24
Lower large intestine wall	8.99±0.97
Small intestine	3.04±0.33
Stomach wall	3.00±0.27
Upper large intestine wall	6.86±0.6
Heart Wall	10.5±1.71
Kidneys	9.19±1.27
Liver	5.07±0.58
Lungs	2.48±0.16
Muscle	0.26±0.24
Ovaries	3.04±0.33
Pancreas	3.25±0.24
Red marrow	2.54±0.21
Osteogenic cells	3.82±0.38
Skin	2.10±0.22
Spleen	3.31±0.54
Testes	2.52±0.27
Thymus	2.74±0.24
Thyroid	2.60±0.27
Urinary bladder wall	2.95±0.30
Uterus	3.14±0.33
Total body	2.82±0.22
Effective dose equivalent	4.38 $\mu\text{Sv}/\text{MBq}$
Effective dose	3.70 $\mu\text{Sv}/\text{MBq}$