

UC Irvine

UC Irvine Previously Published Works

Title

Human biodistribution and dosimetry of [18F]nifene, an $\alpha 4\beta 2^*$ nicotinic acetylcholine receptor PET tracer

Permalink

<https://escholarship.org/uc/item/8sx4b3t3>

Journal

Nuclear Medicine and Biology, 55

ISSN

0969-8051

Authors

Betthauser, Tobey J

Hillmer, Ansel T

Lao, Patrick J

et al.

Publication Date

2017-12-01

DOI

10.1016/j.nucmedbio.2017.08.001

Peer reviewed



Published in final edited form as:

Nucl Med Biol. 2017 December ; 55: 7–11. doi:10.1016/j.nucmedbio.2017.08.001.

Human biodistribution and dosimetry of [^{18}F]nifene, an $\alpha 4\beta 2^*$ nicotinic acetylcholine receptor PET tracer

Tobey J Betthausen^{1,2}, Ansel T Hillmer³, Patrick J Lao^{1,2}, Emily Ehlerding¹, Jogeshwar Mukherjee⁴, Charles K. Stone⁵, and Bradley T Christian^{1,2}

¹Department of Medical Physics, University of Wisconsin – Madison School of Medicine and Public Health, Madison, WI, USA

²Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin – Madison School of Medicine and Public Health, Madison, WI, USA

³Departments of Radiology and Biomedical Imaging; Psychiatry; Yale School of Medicine, New Haven, CT, USA

⁴Preclinical Imaging, Department of Radiological Sciences, University of California – Irvine, Irvine, CA, USA

⁵Department of Medicine, University of Wisconsin – Madison School of Medicine and Public Health, Madison, WI, USA

Abstract

Introduction—The $\alpha 4\beta 2^*$ nicotinic acetylcholine receptor (nAChR) system is implicated in many neuropsychiatric pathologies. [^{18}F]Nifene is a positron emission tomography (PET) ligand that has shown promise for in vivo imaging of the $\alpha 4\beta 2^*$ nAChR system in preclinical models and humans. This work establishes the radiation burden associated with [^{18}F]nifene PET scans in humans.

Methods—Four human subjects (2M, 2F) underwent whole-body PET/CT scans to determine the human biodistribution of [^{18}F]nifene. Source organs were identified and time-activity-curves (TACs) were extracted from the PET time-series. Dose estimates were calculated for each subject using OLINDA/EXM v1.1.

Results—[^{18}F]Nifene was well tolerated by all subjects with no adverse events reported. The mean whole-body effective dose was 28.4 ± 3.8 mSv/MBq without bladder voiding, and 22.6 ± 1.9 mSv/MBq with hourly micturition. The urinary bladder radiation dose limited the maximum injected dose for a single scan to 278 MBq without urinary bladder voiding, and 519 MBq with hourly voiding.

Corresponding Author: Tobey J Betthausen, Department of Medical Physics, University of Wisconsin – Madison Waisman Brain Imaging and Behavior, 1500 Highland Avenue, Rm T229, Madison, WI, 53705, Tel: +1 (608)-890-2959; Fax: +1 (608)-262-9440.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—[¹⁸F]Nifene is a safe PET radioligand for imaging the $\alpha 4\beta 2^*$ nAChR system in humans.

Keywords

Nicotinic Acetylcholine; Positron Emission Tomography; Dosimetry

INTRODUCTION

The nicotinic acetylcholine receptor (nAChR) system is responsible for brain functions such as learning, memory, and cognition. The $\alpha 4\beta 2$ nAChR subtype is the most abundantly distributed subtype in the brain and is implicated in neuropsychiatric pathologies such as neurodegenerative disease and drug addiction [1]. Positron emission tomography (PET) imaging of $\alpha 4\beta 2$ nAChRs with 2-[¹⁸F]FA-85380 [2] and the single photon emission computed tomography (SPECT) counterpart 5-[¹²³I]IA-85380 [3] has yielded important findings in areas such as Alzheimer's disease [4] and tobacco addiction [5]. Owing largely to the successes of these radiotracers, second generation PET tracers are continuing to be developed and evaluated for in vivo characterization of $\alpha 4\beta 2$ nAChRs that improve upon slow kinetics of 2-[¹⁸F]FA-85380. [¹⁸F]Nifene is a second-generation $\alpha 4\beta 2$ nAChR radioligand with fast kinetic properties that have been evaluated in preclinical models (mice, rats and rhesus macaques) [6–12]. Recently, [¹⁸F]nifene was evaluated in humans for the first time, demonstrating suitable *in vivo* specific binding in $\alpha 4\beta 2^*$ nAChR dense regions with rapid kinetics resulting in reliable binding estimates from as little as 40 minutes of dynamic acquisition [13]. Preclinical dosimetry and toxicology performed in mice and extrapolated to humans suggested [¹⁸F]nifene doses of up to 850 MBq are within human radiation dose limits [9]. Given the promising neuroimaging results of [¹⁸F]nifene, the goal of this work is to utilize whole body (WB) PET/computerized tomography (CT) scans in human subjects to characterize and confirm the WB biodistribution and estimate the radiation burden of [¹⁸F]nifene in humans.

MATERIALS AND METHODS

Study Participants

Four participants (2M, 2F) aged 27 to 78 years were recruited for whole-body PET/CT imaging. Individuals were included for the study if they were between the ages of 18–88 years and had a BMI of 22–28. Participants were excluded from the study if they were taking medication that would directly interact with the $\alpha 4\beta 2^*$ nAChR system, were pregnant or nursing, or had participated in the brain characterization portion related to this human evaluation study. Prior to imaging, participants underwent a medical history evaluation, physical examination, echocardiogram, and blood and urine were collected for a blood chemistry profile, complete blood count, and urinalysis. Nonpregnant status was determined by a urine test for females. Vital signs were monitored once participants were positioned on the scanner bed and repeated periodically for a minimum of two hours after injection of [¹⁸F]nifene. Following the PET scan, the pre-scan tests were repeated with the exception of the medical history review and pregnancy test. Written informed consent was obtained from all individuals prior to participation in the study. All human studies were performed under

the University of Wisconsin – Madison Institutional Review Board approval and United States Food and Drug Administration approved investigational new drug application.

PET/CT Imaging

[¹⁸F]Nifene was synthesized at the University of Wisconsin Waisman Center according to previously reported methods [7]. Imaging data were acquired on a Discovery 710 PET/CT (GE Healthcare) at the University of Wisconsin Institute of Medical Research. Prior to imaging, participants were positioned supine with arms at their sides and immobilized. A low-dose computed tomography (CT) scan was obtained and used for anatomical ROI delineation and PET attenuation correction. Whole body PET acquisition commenced with bolus injection of a 189 ± 8 MBq dose of [¹⁸F]nifene administered in the antecubital vein. WB PET scans consisting of eight bed positions each were acquired starting with bolus injection (30 s/bed), and at 10 (30 s/bed), 21 (1 min/bed), 36 (2 min/bed), and 59 (3 min/bed) minutes post injection, spanning spatially from the top of the head to mid-thigh. Two subjects were scanned head to thigh and the direction was reversed for the remaining two subjects. Participants remained immobilized for the entire duration of the study to avoid registration errors.

PET Data Analysis and Residence Time Calculation

PET Processing and Data Extraction—PET data were reconstructed using OSEM (Vue Point FX-TOF, 3 iterations, 24 subsets, 4.4 mm Gaussian smoothing, $192 \times 192 \times 299$ matrix, and $3.65 \times 3.65 \times 3.27$ mm) and corrected for attenuation (CT-based), scatter, deadtime, and radioactive decay to the beginning of bolus injection. Regions of interest (ROIs) were hand drawn on CT images for source organs that indicated elevated uptake relative to background, which included brain, gallbladder, heart, kidneys, liver, lower large intestine, lungs, muscle (ROI in gluteal muscle), pancreas, small intestine, red marrow (ROI in lumbar spine), spleen, stomach, and urinary bladder. ROIs were drawn proximal to organ boundaries to mitigate partial volume effects. Time-activity curves (TACs) were extracted for all source organs. In the case where an organ spanned multiple bed positions, multiple time points were included in TACs, one for each bed position.

Residence Time Calculation—TACs normalized to injected radioactivity and body mass (standard uptake value, SUV) were fit to one of three exponential models based on the shape of the SUV TACs and expected physiological clearance using code developed in our lab (MATLAB 2015a). Fitting parameters were used to generate model data incorporating radioactive decay with one-minute sampling intervals for each source organ spanning a total of ten F-18 half-lives (1090 min, representing >99.99% of all decays) assuming extrapolated values beyond the scan duration. Residence times for each organ were calculated by integrating the model SUV data (trapezoidal method) and multiplying by the ratio of organ mass to the whole body mass. The residence time for the rest of the body was determined by subtracting the residence time of ¹⁸F in hours (2.64 hours) from the sum of all source organ residence times.

Radiation Dose Estimation

OLINDA software (V1.1) was used to estimate organ and whole body effective radiation dose [14]. Residence times were entered into OLINDA for all source organs and dose estimates were obtained using the hermaphroditic adult phantom [15]. Since urinary bladder voiding was not performed during the study, a voiding model was implemented in OLINDA. The bladder-voiding model assumed hourly micturition following injection of the radiotracer, and used parameter estimates from the residence time calculation to determine the excretion fraction and biological half-life of the urinary clearance. Dose estimates are reported both with and without the use of the bladder-voiding model.

RESULTS

There were no adverse events or clinically significant changes observed during the course of this study. SUV TACs for all source organs are provided in Figure 1. Dosimetry estimates and visual assessment of whole body images indicated the renal pathway as the primary clearance mechanism of [^{18}F]nifene (Figure 2). Parameterization of the urinary bladder clearance indicated a mean %ID of $35\% \pm 10\%$ with a mean biological half-life of 19 ± 10 min. In the older male subject, high retention was observed in the gallbladder, but this was not observed in other subjects.

Table 1 gives the average residence times for male and female subjects for all source organs including the urinary bladder with and without voiding. Human dosimetry estimates are given for the hermaphroditic male phantom in Table 2. The highest organ dose was observed in the urinary bladder wall ($1.80\text{E-}01$ mSv/MBq without voiding, $9.64\text{E-}02$ mSv/MBq with bladder voiding), followed by the kidneys, small intestine, gallbladder wall and liver. The mean effective dose across the four subjects was 24.9 ± 4.3 $\mu\text{Sv/MBq}$.

DISCUSSION

Radiation Dose in Humans

These data provide measurements of the WB biodistribution and source organ residence times of [^{18}F]nifene in four subjects, which were used to estimate the radiation burden of [^{18}F]nifene in humans. Radiation dose limits specified in 21 CFR 361.1 sets maximum doses of three rem per scan for whole body, blood-forming organs, lens of the eye, and gonads, and five rem per scan for other organs. In this context, the urinary bladder is the dose-limiting organ for [^{18}F]nifene. Based on the maximum allowable dose of five rem for the urinary bladder, the maximum injected dose is 278 MBq (7.5 mCi) without bladder voiding, and 519 MBq (14 mCi) when bladder voiding is performed hourly following dose administration. Previous human neuroimaging studies performed by our group [13] indicate that a 185 MBq injection of [^{18}F]nifene is sufficient to obtain accurate binding estimates in the brain, which would result in a WB effective dose of 0.5 rem and a urinary bladder dose of 3.33 rem per scan (1.78 rem with hourly voiding). This would allow for up to four 185 MBq [^{18}F]nifene scans within the period of a year, which is beneficial for studies that might require baseline and subsequent follow-up scans.

Comparison with mouse data

The biodistribution of [^{18}F]nifene has been previously studied in BALB/c mice and dose estimates were extrapolated to humans [9]. Overall, the preclinical biodistribution was consistent between species. However, the magnitude of the dose estimates was lower using the data from mice, particularly for clearance organs (urinary bladder, kidneys, and gastrointestinal organs). In most organs, human dose estimates derived from mouse data were lower ($-19\% \pm 31\%$ mean difference across all organs) than dose estimates derived from human subjects. Additionally, the whole body effective dose was 37% lower using mouse data. However, when the interspecies comparison was made implementing the bladder-voiding model in humans, the dose estimates between species showed better agreement ($-15\% \pm 29\%$ mean difference across all organs, WB effective dose was 21% lower in mouse data). This suggests that differences in renal clearance are responsible for a considerable amount of the discrepancies between species. Mice models provide good initial estimates of radiotracer dosimetry, however the differences between mouse and human dose estimates highlight the need for confirmation of dosimetry in the species intended for study.

Comparison with other human $\alpha 4\beta 2$ tracers

Human dosimetry studies have been performed for several ^{18}F -labeled $\alpha 4\beta 2^*$ nAChR PET tracers [16–18] and are compared to [^{18}F]nifene in Figure 3. Overall, individual organ doses and whole body effective doses are similar between the various radiotracers with the greatest differences present in the urinary bladder wall. When bladder voiding is performed, the urinary bladder wall dose is only slightly higher for [^{18}F]nifene when compared to 2- [^{18}F]FA, [^{18}F]Flubatine, and [^{18}F]AZAN. A recent study performed in mice and extrapolated to humans [19] suggests another second-generation $\alpha 4\beta 2^*$ PET tracer ([^{18}F]XTRA) has a urinary bladder wall dose nearly five times higher than other ^{18}F -labeled tracers. When considering kinetics and imaging characteristics of the various tracers that have been studied in humans, an advantage of [^{18}F]nifene is the rapid kinetics, which results in short scan durations (~ 40 min dynamic scan) for quantification of neuroreceptor binding. Shorter scans are beneficial for dosimetry, as bladder voiding can be performed more quickly after injection of the tracer.

CONCLUSIONS

This work used WB PET/CT to measure the radiation dose associated with [^{18}F]nifene studies. Dosimetry estimates indicate the bladder to be the dose limiting organ, where hourly bladder voiding allows for a maximum injected dose of 278 MBq [^{18}F]nifene, or up to four 185 MBq [^{18}F]nifene scans annually. These findings support [^{18}F]nifene as a safe PET radioligand for imaging the $\alpha 4\beta 2^*$ nAChR system in humans.

Acknowledgments

Special thanks to the UW Cyclotron Group, Ryan O'Hearn and the UW Office of Clinical Trials and the technologists at the Wisconsin Institute of Medical Research PET Lab.

Funding

Support for this work was provided by the National Institute of Health R01 AG029479, the National Institute on Child Health and Human Development U54 HD090256, the National Cancer Institute of the National Institutes of Health under Award Number T32 CA009206, and the National Institute of General Medical Sciences of the National Institutes of Health under Award Number T32 GM008505.

References

1. Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. *Prog Neurobiol.* 2004; 74:363–96. [PubMed: 15649582]
2. Gallezot JD, Bottlaender M, Gregoire MC, Roumenov D, Deverre JR, Coulon C, et al. In vivo imaging of human cerebral nicotinic acetylcholine receptors with 2-18F-fluoro-A-85380 and *PET*. *J Nucl Med.* 2005; 46:240–7. [PubMed: 15695782]
3. Fujita M, Ichise M, van Dyck CH, Zoghbi SS, Tamagnan G, Mukhin AG, et al. Quantification of nicotinic acetylcholine receptors in human brain using [123I]5-I-A-85380 SPET. *Eur J Nucl Med Mol Imaging.* 2003; 30:1620–9. [PubMed: 14523584]
4. Kendziorra K, Wolf H, Meyer PM, Barthel H, Hesse S, Becker GA, et al. Decreased cerebral alpha4beta2* nicotinic acetylcholine receptor availability in patients with mild cognitive impairment and Alzheimer's disease assessed with positron emission tomography. *Eur J Nucl Med Mol Imaging.* 2011; 38:515–25. [PubMed: 21069319]
5. Cosgrove KP, Batis J, Bois F, Maciejewski PK, Esterlis I, Kloczynski T, et al. beta2-Nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. *Arch Gen Psychiatry.* 2009; 66:666–76. [PubMed: 19487632]
6. Hillmer AT, Wooten DW, Moirano JM, Slesarev M, Barnhart TE, Engle JW, et al. Specific alpha4beta2 nicotinic acetylcholine receptor binding of [F-18]nifene in the rhesus monkey. *Synapse.* 2011; 65:1309–18. [PubMed: 21674627]
7. Hillmer AT, Wooten DW, Slesarev MS, Ahlers EO, Barnhart TE, Murali D, et al. PET imaging of alpha4beta2* nicotinic acetylcholine receptors: quantitative analysis of 18F-nifene kinetics in the nonhuman primate. *J Nucl Med.* 2012; 53:1471–80. [PubMed: 22851633]
8. Hillmer AT, Wooten DW, Slesarev MS, Ahlers EO, Barnhart TE, Schneider ML, et al. Measuring $\alpha 4 \beta 2^*$ Nicotinic Acetylcholine Receptor Density in Vivo with [18F] nifene PET in the Nonhuman Primate. *Journal of Cerebral Blood Flow & Metabolism.* 2013; 33:1806–14. [PubMed: 23942367]
9. Constantinescu CC, Garcia A, Mirbolooki MR, Pan ML, Mukherjee J. Evaluation of [18F]Nifene biodistribution and dosimetry based on whole-body PET imaging of mice. *Nucl Med Biol.* 2013; 40:289–94. [PubMed: 23265670]
10. Hillmer AT, Wooten DW, Farhoud M, Barnhart TE, Mukherjee J, Christian BT. The effects of lobeline on alpha4beta2* nicotinic acetylcholine receptor binding and uptake of [(18)F]nifene in rats. *J Neurosci Methods.* 2013; 214:163–9. [PubMed: 23370310]
11. Hillmer AT, Tudorascu DL, Wooten DW, Lao PJ, Barnhart TE, Ahlers EO, et al. Changes in the alpha4beta2* nicotinic acetylcholine system during chronic controlled alcohol exposure in nonhuman primates. *Drug Alcohol Depend.* 2014; 138:216–9. [PubMed: 24602361]
12. Pichika R, Easwaramoorthy B, Collins D, Christian BT, Shi B, Narayanan TK, et al. Nicotinic alpha4beta2 receptor imaging agents: part II. Synthesis and biological evaluation of 2-[18F]fluoro-3-[2-((S)-3-pyrrolinyl)methoxy]pyridine (18F-nifene) in rodents and imaging by PET in nonhuman primate. *Nucl Med Biol.* 2006; 33:295–304. [PubMed: 16631077]
13. Lao PJ, Betthausen TJ, Tudorascu DL, Barnhart TE, Hillmer AT, Stone CK, et al. [18 F]Nifene test-retest reproducibility in first-in-human imaging of alpha4beta2* nicotinic acetylcholine receptors. *Synapse.* 2017
14. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med.* 2005; 46:1023–7. [PubMed: 15937315]
15. Cristy, M., Eckerman, K. Specific absorbed fractions of energy at various ages from internal photon sources. 1987. p. 3ORNL/TM-8381
16. Bottlaender M, Valette H, Roumenov D, Dolle F, Coulon C, Ottaviani M, et al. Biodistribution and radiation dosimetry of 18F-fluoro-A-85380 in healthy volunteers. *J Nucl Med.* 2003; 44:596–601. [PubMed: 12679405]

17. Kranz M, Sattler B, Tiepolt S, Wilke S, Deuther-Conrad W, Donat CK, et al. Radiation dosimetry of the alpha4beta2 nicotinic receptor ligand (+)-[18F]flubatine, comparing preclinical PET/MRI and PET/CT to first-in-human PET/CT results. *EJNMMI Phys.* 2016; 3:25. [PubMed: 27770429]
18. Wong DF, Kuwabara H, Kim J, Brasic JR, Chamroonrat W, Gao Y, et al. PET imaging of high-affinity alpha4beta2 nicotinic acetylcholine receptors in humans with 18F-AZAN, a radioligand with optimal brain kinetics. *J Nucl Med.* 2013; 54:1308–14. [PubMed: 23801676]
19. Kuwabara H, Gao Y, Stabin M, Coughlin J, Nimmagadda S, Dannals RF, et al. Imaging alpha4beta2 Nicotinic Acetylcholine Receptors (nAChRs) in Baboons with [18F]XTRA, a Radioligand with Improved Specific Binding in Extra-Thalamic Regions. *Mol Imaging Biol.* 2017; 19:280–8. [PubMed: 27562686]

Advances in Knowledge and Implications for Patient Care

This work presents human internal dosimetry for [^{18}F]nifene in humans for the first time. These results facilitate safe development of future [^{18}F]nifene studies to image the $\alpha 4\beta 2^*$ nAChR system in humans.

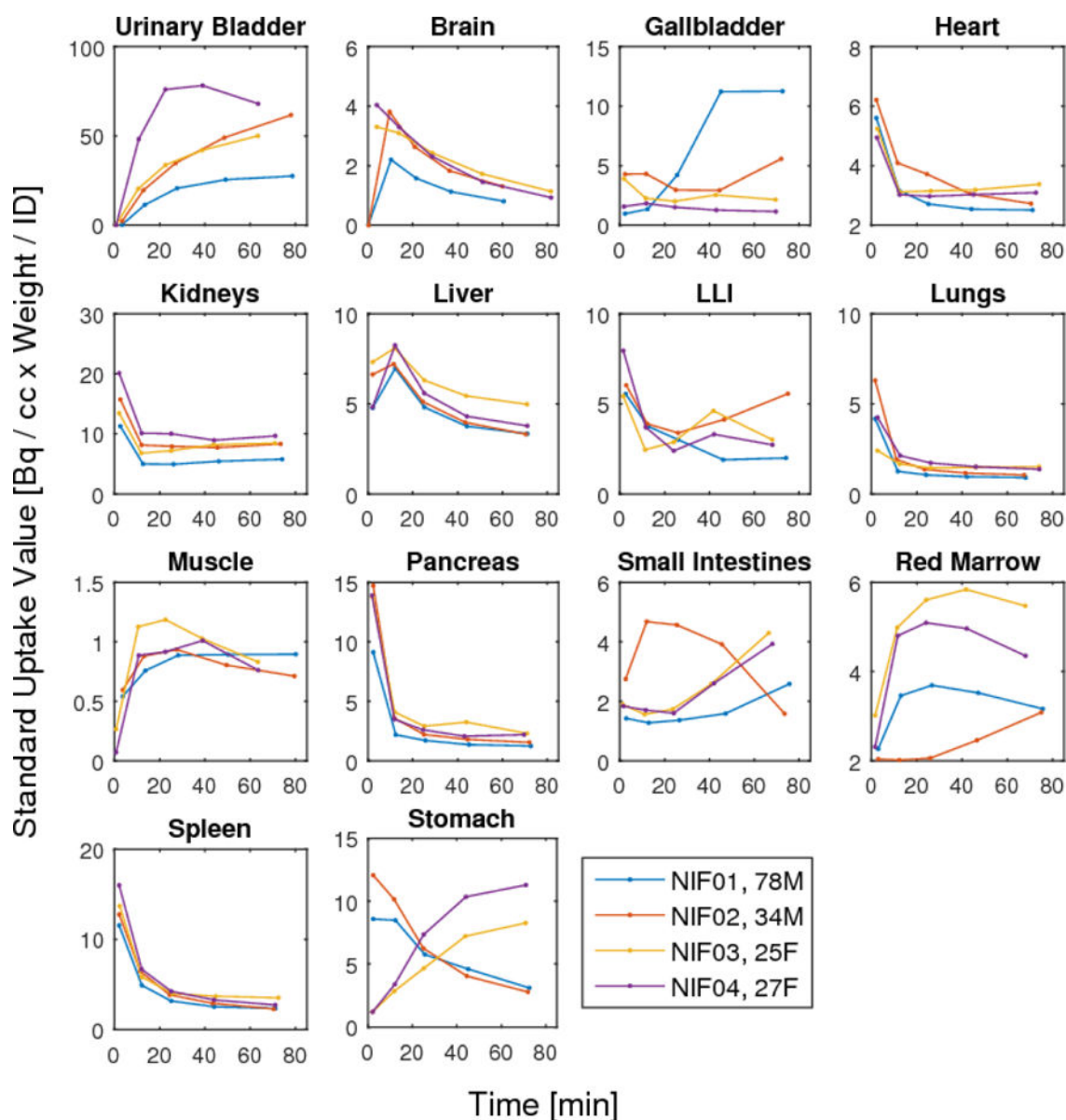


Figure 1. Source Organ Time-Activity Curves of $[^{18}\text{F}]$ nifene in Humans

TACs normalized to body weight and injected dose (SUV) indicate the highest uptake in the urinary bladder. Each color represents an individual human subject. For detailed brain region kinetics, see reference [17]. (LLI = lower large intestine)

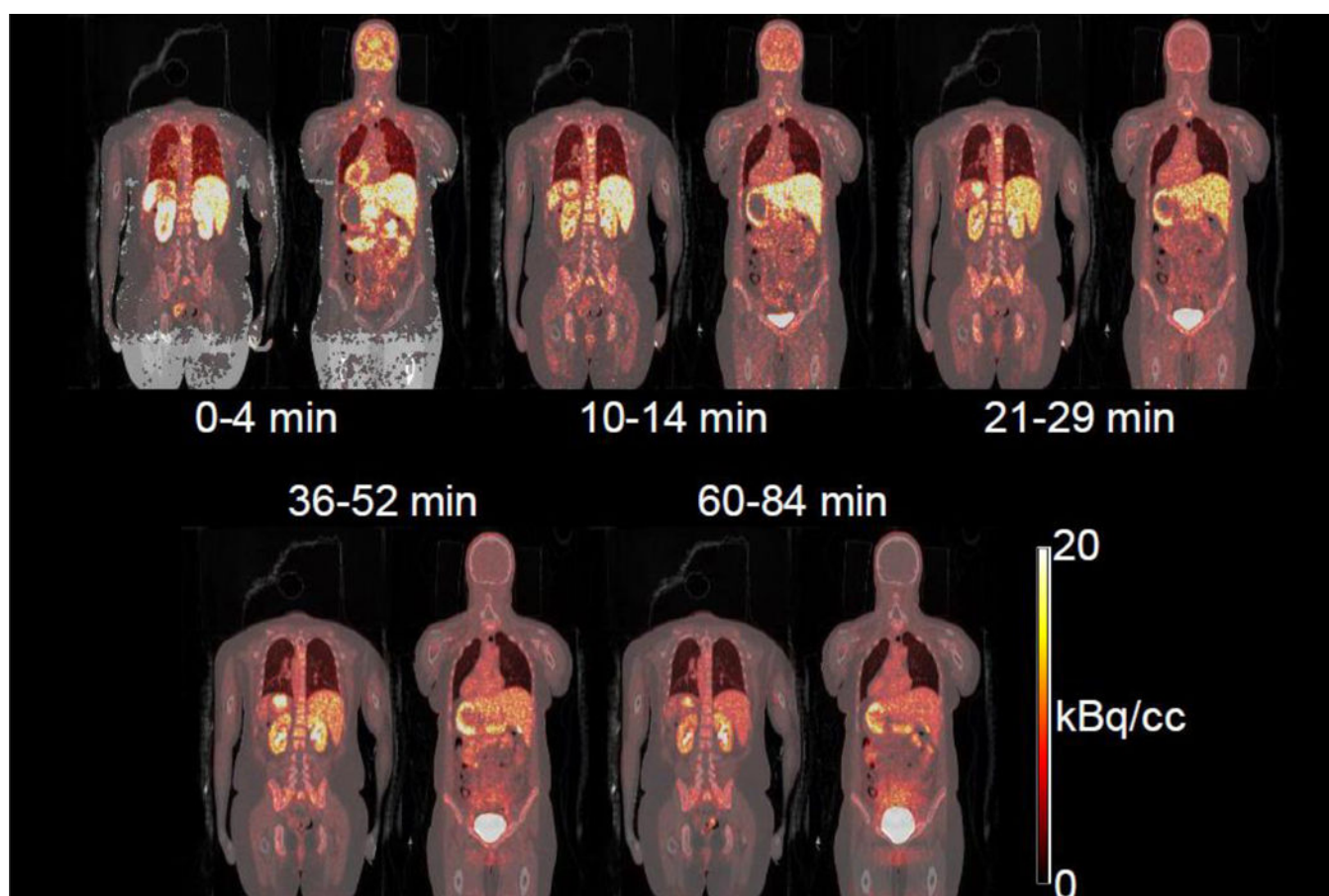


Figure 2. Whole Body Biodistribution of [^{18}F]nifene in Humans

PET time series images showing the biodistribution of [^{18}F]nifene over the PET scan duration in a single female participant that received a 183MBq injection. Two coronal images are shown for each WB PET frame to adequately illustrate all source organs.

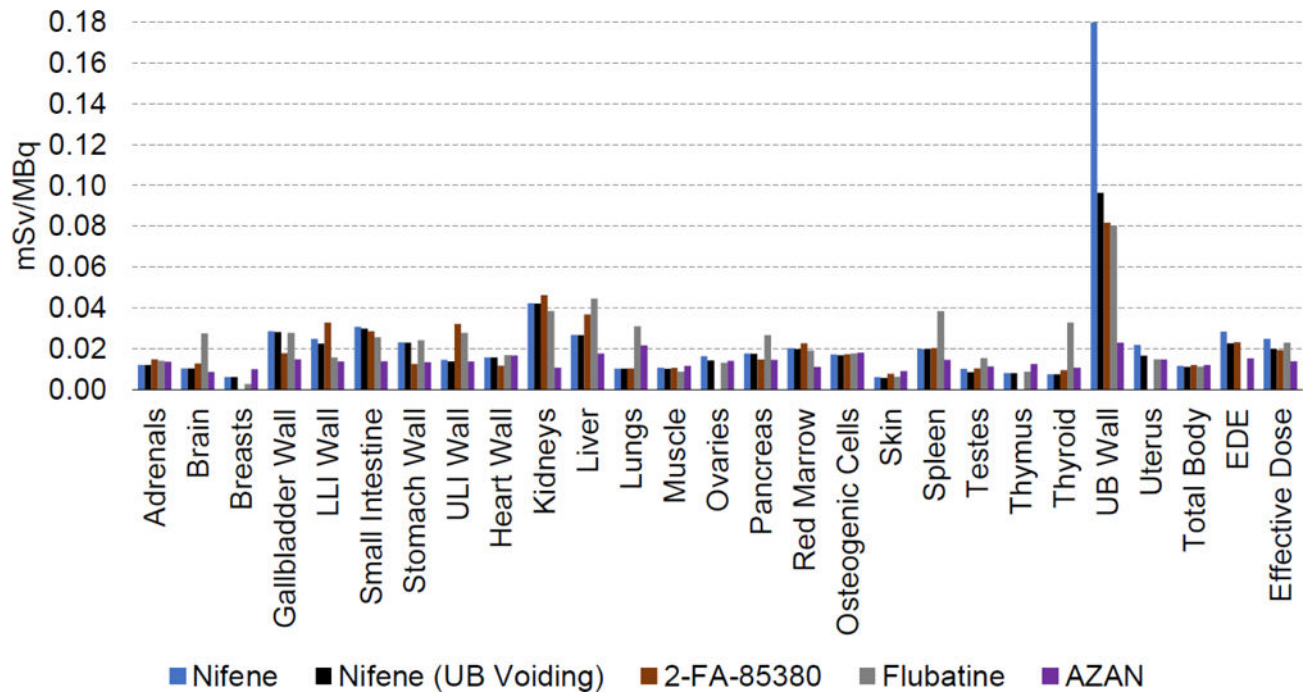


Figure 3. Comparison of $\alpha 4\beta 2^*$ nAChR PET Radioligand Dosimetry Estimates

Human organ dose estimates using [^{18}F]nifene were similar to other ^{18}F -labeled $\alpha 4\beta 2^*$ nAChR PET radioligands [16–19]. All dose estimates are derived from human data. (LLI = lower large intestine, ULI = upper large intestine, UB = urinary bladder, EDE = effective dose equivalent)

Table 1
Source Organ Residence Times

Mean residence times of the four subjects that received WB [^{18}F]nifene PET scans (mean $\pm$ standard deviation). Rest of body was determined by subtracting the sum of the source organ residence times from the theoretical residence time of F-18. The urinary bladder with voiding assumes hourly micturition upon injection of the tracer.

Organ	Residence Time [h]
Brain	0.050 ± 0.014
Gallbladder Contents	0.010 ± 0.008
Heart Contents	0.032 ± 0.004
Kidneys	0.057 ± 0.017
Liver	0.177 ± 0.019
Lower Large Intestine	0.017 ± 0.009
Lung	0.026 ± 0.009
Muscle	0.684 ± 0.076
Pancreas	0.004 ± 0.002
Small Intestine Contents	0.097 ± 0.022
Red Marrow	0.162 ± 0.062
Spleen	0.012 ± 0.002
Stomach	0.037 ± 0.026
Urinary Bladder (no voiding)	0.363 ± 0.122
Urinary Bladder (with voiding)	0.186 ± 0.056
Rest of Body	0.914 ± 0.137

Table 2
Human Radiation Dose Estimates

Mean dose estimates (mean $\pm$ standard deviation) for [^{18}F]nifene in humans without bladder voiding (second column) and with hourly urinary bladder voiding (third column). Results are given as the mean $\pm$ standard deviation across the four subjects that underwent WB PET scans, and were determined using the hermaphroditic adult phantom. (LLI = lower large intestine, ULI = upper large intestine)

Organ	Dose [$\mu\text{Sv}/\text{MBq}$]	Dose with Voiding [$\mu\text{Sv}/\text{MBq}$]
Adrenals	12.10 $\pm$ 0.56	12.03 $\pm$ 0.57
Brain	10.41 $\pm$ 2.19	10.41 $\pm$ 2.19
Breasts	6.22 $\pm$ 0.50	6.20 $\pm$ 0.51
Gallbladder Wall	28.53 $\pm$ 12.99	28.30 $\pm$ 13.06
LLI Wall	24.93 $\pm$ 5.82	22.53 $\pm$ 4.82
Small Intestine	30.80 $\pm$ 4.39	29.90 $\pm$ 4.35
Stomach Wall	23.10 $\pm$ 9.37	22.95 $\pm$ 9.38
ULI Wall	14.53 $\pm$ 0.79	13.83 $\pm$ 0.94
Heart Wall	15.78 $\pm$ 0.80	15.78 $\pm$ 0.80
Kidneys	42.28 $\pm$ 10.08	42.13 $\pm$ 10.00
Liver	26.75 $\pm$ 2.31	26.65 $\pm$ 2.31
Lungs	10.30 $\pm$ 1.52	10.30 $\pm$ 1.52
Muscle	10.73 $\pm$ 0.38	10.13 $\pm$ 0.59
Ovaries	16.45 $\pm$ 1.11	14.23 $\pm$ 0.52
Pancreas	17.60 $\pm$ 3.92	17.50 $\pm$ 3.92
Red Marrow	20.30 $\pm$ 4.18	19.90 $\pm$ 4.20
Osteogenic Cells	17.20 $\pm$ 1.94	16.98 $\pm$ 1.94
Skin	6.01 $\pm$ 0.39	5.80 $\pm$ 0.48
Spleen	19.83 $\pm$ 2.96	19.75 $\pm$ 2.92
Testes	10.17 $\pm$ 0.61	8.55 $\pm$ 0.64
Thymus	8.15 $\pm$ 0.60	8.14 $\pm$ 0.61
Thyroid	7.47 $\pm$ 0.73	7.46 $\pm$ 0.73
Urinary Bladder Wall	179.75 $\pm$ 56.67	96.40 $\pm$ 25.73
Uterus	21.88 $\pm$ 2.90	16.60 $\pm$ 1.17
Total Body	11.68 $\pm$ 0.17	11.18 $\pm$ 0.43
Effective Dose Equivalent	28.38 $\pm$ 3.77	22.63 $\pm$ 1.88
Effective Dose	24.90 $\pm$ 4.30	19.88 $\pm$ 2.55