Optimized uptake time of $^{18}$F-THK5351 PET/CT in normal Thai brain

Pachara Thonglim, Chanisa Chotipanich and Prathan Buranasiri

1 Department of Physics, Faculty of Science, King Mongkut’s Institute of Technology Ladkrabang, Bangkok 10520, Thailand
2 Division of Nuclear Medicine, National Cyclotron and PET Centre, Chulabhorn Hospital, Bangkok 10210, Thailand

E-mail: prathan.bu@kmitl.ac.th

Keywords: $^{18}$F-THK5351, positron emission tomography–computed tomography (PET/CT), optimized uptake time, discrete time, continuous time, Alzheimer’s disease (AD), ana75_2m.mat

Supplementary material for this article is available online

Abstract

This study investigated $^{18}$F-THK5351 positron emission tomography–computed tomography (PET/CT) images to determine the optimized imaging time of radiopharmaceutical PET/CT in normal Thai population. Seventeen volunteers without any neurological or psychiatric illnesses, who showed no abnormalities upon neurological examination and the standardized uptake value ratio, were included. All subjects were diagnosed using $^{18}$F-THK5351 PET/CT and 3.0 Tesla magnetic resonance imaging (MRI). THK5351 PET/CT was operated on the co-registered MRI to draw a region of interest (ROI). A digital imaging and communications in a medical file were converted to a .img file. Next, the image file was rendered from discrete time to continuous time for plotting graphs. The ROI positions and rendered file were then used to plot a graph showing the relationship between the radiopharmaceutical uptake quantity and the interval time to determine the optimized uptake time of THK5351 PET/CT for the brains of normal Thai population, which was consequently 40–60 min.

1. Introduction

Tau proteins are associated with cognitive impairment [1]. The hyperphosphorylation of tau proteins results in pathogenesis frontotemporal dementia, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and chronic traumatic encephalopathy [2–7]. The combination of neurological conditions caused by the accumulation of tau proteins are called tauopathies.

Positron emission tomography–computed tomography (PET-CT) is a potential nuclear medicine technology for tau protein aggregation in the brain. Initially, PET has become a powerful scientific and clinical tool for investigating biochemical processes in vivo, with its clinically effectiveness to detect cancers and neurological diseases, in particular the accurate diagnosis of the pre-clinical stage of Alzheimer’s disease (AD). Previous studies that focused on designing of tau imaging PET radiotracers have led to the development of several types of radiopharmaceuticals for use in humans, such as $^{18}$F-FDDNP [8], $^{18}$F-T808 [9], and $^{18}$F-THK5351 [10].

$^{18}$F-THK5351 can be used to accurately differentiate between patients with AD and normal individuals. A positron-emitting radionuclide is inserted via a radioactive tracer, with the emitted positrons to create a PET image. However, PET requires a considerable amount of time to acquire a suitable image. Thus, this study aimed to determine an optimized uptake time of $^{18}$F-THK5351 PET/CT for a database of proper diagnosis with radiopharmaceutical PET/CT in normal Thai population.

2. Materials and methods

2.1. Radiosynthesis of $^{18}$F-THK5351

$^{18}$F-THK5351 was prepared from its tosylate precursor (S)-2-(2-methylaminopyrid-5-yl)-6-[[2-(tetrahydro-2H-pyran-2-yloxy)-3-tosyloxy]propoxy] quinoline (THK5352) and purified using semipreparative
rays (18F-THK5351 was then obtained with a radiochemical yield of 46% ± 13%, purity of greater than 95%, and specified activity of 254 ± 47 GBq mmol⁻¹ [11]. The radiopharmaceutical systematic name was 2-propanol,1-(fluoro-18F)-3-((2-(6-(methylamino)-3-pyridinyl)-6-quinolinyl)oxy)-, (2 S). The common names were THK-5351 F-18, (18F)(s)-THK-5351, or (18 F)THK-5351. The code name was J3.349.112 C. In figure 1, the structure of 18F-THK5351 was shown with a single S-enantiomer to improve the pharmacokinetics of aryl-quinoline derivatives [12]. THK5351 was used as a tracer for attaching to tau proteins in the brain [13].

2.2. Clinical PET study subjects
A retrospective analysis was conducted in 17 subjects (male, n = 7; female, n = 10; mean age: 58.92 years; range: 41–80 years) to diagnose whether the brain was relatively constant. No neurological and psychiatric illnesses and abnormalities were observed upon the study criteria. The Montreal cognitive assessment (MoCA) and the cut point of quantitative uptake value by PMOD software (PMOD Technologies Ltd, Adliswil, Switzerland) were applied as criteria to distinguish normal and abnormal samples. To pass the MoCA test, a score of more than 25 points had to be achieved from representative samples. Those with AD dementia met the probable AD criteria proposed by the Helen Wills Neuroscience Institute, University of California Berkeley [14], with a standardized uptake value ratio (SUVR) of 40–60 min. Without fasting, all subjects underwent the assessment of true brain region THK5351 PET/CT between October 2017 and January 2018. Prior the acquisition of brain data, each subject was injected with 5 mCi (185 MBq) THK5351. Following the standard protocols, emission data were acquired from the brain region in the 3D dynamic scanning list mode for a fixed time of 20 min in the head first supine position. The obtained PET/CT scans were then anonymized to avoid demographic bias. This study received approval from Human Research Ethics Committee of Chulabhorn Research Institute (Project code: 050/2560).

2.3. PET and MR image acquisition
2.3.1. PET imaging
All PET scans were acquired using Siemens Biograph 16 True-point PET/computed tomography scanner (Siemens Healthineers, USA) with the list mode emission acquisition. Whereas, 18F-THK5351 was synthesized and radiolabelled at National Cyclotron and PET Centre, Chulabhorn Hospital. All subjects underwent the 90-min emission scan after the 5 mCi (185 MBq) of 18F-THK5351 was injected intravenously (0–90 min), with the 3D scanning mode of Siemens Biograph 16 PET/CT system. Then, the THK5351 PET/CT images of the skull were acquired and reconstructed in the 168 × 168 × 81 matrix with the voxel size of 4.06 × 4.06 × 2 mm, zoom = 1, Gaussian filter with FWHM = 2.0, and THK5351 PET/CT, as shown in figure 2. After intravenous injection, the radioactive 18F-THK5351 decayed to produce positrons [15]. Meanwhile, the positron-electron annihilation in vivo produced positronium [16, 17]. The decayed positronium finally generated a pair of gammas rays (γ), each with the energy of 0.551 MeV [18], which travelled in opposite directions and detected by the gamma ray detector of PET/CT (figure 3).

2.3.2. MR imaging acquisition
The 3DT1-magnetization-prepared rapid gradient echo (repetition time: 1900 ms, echo time: 2.93 ms, flip angle: 8°, pixel bandwidth: 170 Hz/pixel, matrix size: 256 × 208, field of view: 256 mm, number of excitations: 1, total acquisition time: 4 min 10 s, and voxel size: 0.5 × 0.5 × 1.0 mm³) was acquired with 3.0 T MRI (MAGNETOM Verio, Siemens Healthineers). Those images were used for the subsequent screening of

![Figure 1. Structure of 18F-THK5351.](image)
co-registration with the PET images by PMOD software (see Figure 2). The PMOD software consisted of a comprehensive set of user-friendly and powerful tools, each corresponding to major tasks such as kinetic modelling, parametric mapping, image registration, 3D rendering, and pattern analysis. Due to their smooth interactions, a flexible workbench was formed for all types of research data from humans and other species. Every PET image study was complemented with T1-weighted brain MRIs which precisely represented the subjects’ anatomy. Knowledge-based technology was employed to accurately segment the cortex and the basal ganglia from human T1-MRIs. These segments were then projected onto the PET images and calculated, after which the quantitative analysis could be performed.

2.4. Image analysis

2.4.1. Image reconstruction

The THK5351 PET/CT image was reconstructed after the acquisition of PET/CT image in the form of digital imaging and communications in medicine (DICOM). DCM file. Whilst, the 4-frame image reconstruction was done with 20 min for each frame (0–20, 20–40, 40–60, and 60–80 min). Subsequently, the four frames of DICOM file were converted into an image file (.img) by MRI conversion (Lewis Center for Neuroimaging, University of Oregon, USA). Then, the four frames in the image file were rendered from discrete time to continuous time using ana75_2m.mat (see Figure 4) [19], which was written in a computer language to run on MATLAB_R2016b program (MathWorks, Inc., Massachusetts, USA). Following the main form of PET image reconstruction with 4 separated frames (0–20, 20–40, 40–60, and 60–80 min), ana75_2m.mat (shown as supplementary material is available online at stacks.iop.org/JPCO/3/075011/mmedia) was constructed to render all PET images in the continuous time form of imaging (0–90 min) as MATLAB file (fmridata.mat). The

Figure 2. Image of the brain: (a) T1-weight MRI, (b) THK5351 PET imaging, and (c) MR imaging from subsequent screening of co-registration with PET image by PMOD software.

Figure 3. Positron–electron annihilation.
fmridata.mat contained data of radiopharmaceutical quantity and interval time, but none of the observed brain position.

2.4.2. ROIs
The regions of interest (ROIs) should be required for the observation of brain position to specify any correlations among them by manual or automatic methods. In this study, the ROIs were specified by an automatic method to propagate them from a predefined atlas onto the standard space. A previous study provided a well-known atlas with 10 labelled ROIs \[14\]. THK5351 PET/CT images were applied for the subsequent screening of co-registration with MRI images using PMOD software to draw ROIs. The obtained results of ROIs were represented in Cartesian coordinates \((x, y, z)\). Also, the Anterior commissure was used to set the origin of brain observation \((0, 0, 0)\). The brain positions (10 regions: frontal cortex, fusiform gyrus, inferior temporal cortex, lingual gyrus, middle temporal gyrus, occipital cortex, parahippocampal gyrus, parietal cortex, posterior cingulate, and precuneus) were employed to plot graphs using fmridata.

2.4.3. Graphs representing optimized uptake time of THK5351 PET/CT
After the ROIs were drawn, the selected position in the Cartesian coordinates \((x, y, z)\) was used to plot graphs showing the relationship between the quantitative uptake and the interval time by MATLAB_R2016b. The graphs demonstrated the quantitative uptake of the impulse response of \(^{18}\)F-THK5351 relative to the time series for the optimized uptake time of the radioactive tracer PET/CT. In this process, the position of ROIs \((x, y, z)\) and fmridata.mat were considered to plot graphs using MATLAB code.

```matlab
load fmridata.mat

% file of quantitative uptake from four frames of images

ts = zeros(1, 4); % indication of data from frame 1 to frame 4

% indication of data of quantitative uptake in area of interest for the entire time

plot(ts) % plotting graphs

Graphs representing the optimized uptake time for PET/CT were obtained. Figure 5 showed the experimental process.

2.5. Statistical analysis
Bonferroni correction coefficients were used to understand the relationship between the subject groups and AD dementia. Whereas, 95% confidence intervals were reported where appropriate, with p-values less than 0.05 considered as statistical significance. All statistical analyses were conducted using PASW statistics 23 software (SPSS Inc., Chicago, IL, USA).

3. Results and discussion

3.1. Clinical PET study subjects
All subjects passed the MoCA Thai version test with the average score of 28. After the head first supine THK5351 PET/CT, SUVR was obtained as summarized in table 1. The MoCA was used as a criterion to distinguish abnormal and normal samples. Table 1 demonstrated the values of ROIs for group differences in SUVR 40–60 min between the AD groups in Lockhart’s research \[14\] and the subject groups (Thai population).

Table 1 listed the values for all investigated ROIs. A significant \((p < 0.05)\) group difference was generally observed in temporoparietal regions. The accumulated tau protein in large amount reference position was
changed to pons or thalamus regions. SUVR was used for quantitative analysis and calculated as the uptake ratio of the radioactive tracer between the cortical region and the cerebellum. Lockhart et al. [14] showed that the most precise diagnosis area to distinguish AD patients from normal population was the inferior temporal lobe of SUVR > 1.68 (100%).

3.2. Image processing
The MR images were used in the subsequent screening of co-registration with PET images by PMOD software for the drawn ROIs. The position of ROIs in the Cartesian coordinates was \( (X, Y, Z) \). The brain positions (10 regions) observed in the Cartesian coordinates were listed in table 2.

3.3. Graphs representing imaging time
A graph of the relationship between the radiopharmaceutical uptake quantity in the brain and the interval time for 10 regions was obtained from the results of ROI positions using fmridata.mat. As shown in figures 6(a)–(j),

### Table 1. Values of ROIs for group differences in SUVR 40–60 min.

| ROI                        | AD mean [14] | PP mean | p value  |
|----------------------------|--------------|---------|----------|
| Anterior cingulate         | 1.89         | 1.76    | =0.005a  |
| Brainstem                  | 1.95         | 1.85    | =0.006a  |
| Caudate nucleus            | 2.44         | 1.68    | <0.001b  |
| Eroded white matter        | 1.82         | 1.73    | =0.007a  |
| Entorhinal cortex          | 2.06         | 2.00    | =0.92    |
| Frontal cortex             | 1.48         | 1.45    | =0.68a   |
| Fusiform gyrus             | 1.89         | 1.67    | <0.001b  |
| Hippocampus                | 2.48         | 2.37    | =0.20a   |
| Inferior temporal cortex   | 1.95         | 1.53    | <0.001b  |
| Lingual gyrus              | 1.51         | 1.30    | <0.001b  |
| Middle temporal gyrus      | 1.91         | 1.57    | <0.001b  |
| Occipital cortex           | 1.41         | 1.32    | <0.001b  |
| Pallidum                   | 3.66         | 3.31    | <0.001b  |
| Parahippocampal gyrus      | 1.9          | 1.65    | <0.001b  |
| Parietal cortex            | 1.65         | 1.35    | <0.001b  |
| Posterior cingulate        | 1.93         | 1.61    | <0.001b  |
| Putamen                    | 2.96         | 2.65    | <0.001b  |
| Thalamus                   | 2.83         | 2.40    | <0.001b  |

Key: AD, Alzheimer’s disease; PP, Participants.

\( ^a p < 0.05 \)

\( ^b p < 0.001 \)
The impulse response of 10 regions from the graphs was used to obtain the average information. Equation (1) was implemented as MATLAB code, as shown in figure 7.

\[
\text{average} = \frac{\text{fmridata}_1 + \text{fmridata}_2 + \text{fmridata}_3 + \ldots + \text{fmridata}_{10}}{10}
\]

The main peak corresponding to the radiopharmaceutical uptake quantity was approximately located at an interval time of 3. Whereas, a shoulder indicating an increase and a decrease in the radiopharmaceutical uptake quantity was observed at interval times of 2 and 4, respectively. This increasing and decreasing trend was attributed to the fact that the uptake of the minute amounts of the radioactive tracer still occurred in the brain. Figure 7 illustrated the average impulse response of $^{18}$F-THK5351 PET/CT in normal Thai population. During the interval times of 2 and 4, the radiopharmaceutical uptake quantity in the brain increased from the interval time of 2 to the interval time of 3 (main peak) before a decrease at an interval time of 4. This main peak was applied as the optimized uptake time for the radiopharmaceutical. Consequently, the optimized uptake time for $^{18}$F-THK5351 PET/CT was between 40 and 60 min. Following this optimized uptake time, data could be confirmed with images from the Syngo-via program (Siemens Healthcare GmbH) (figure 8).

To confirm, we further verified the quantitative uptake in the thalamus region [20, 21]. Figure 8 demonstrated the quantitative uptake of $^{18}$F-THK5351 in the thalamus region after the radioactive tracer was injected intravenously. The distribution of $^{18}$F-THK5351 looked uniform in the thalamus region (denoted by yellow, blue, and green arrows in figure 8). The additional time in the thalamus region resulted in the uniformity of this region. A comparison from frames 2 to 4 showed the quantitative uptake clusters. A size-dependent effect was noted in the Thalamus region. The additional amount of $^{18}$F-THK5351 seemed to increase the cluster aggregation from frames 2 to 3 (figures 8(b) and (c)), then gradually decreased to the same in frame 4 (figure 8(d)).

Figure 8(a) illustrated the frames of images after THK5351 was injected for 20 min (frame 1), with a perfusion-like distubution of the radiopharmaceutical following the cortical and the subcortical uptake. As for the brain, the SUV at 20 min after the injection was highest in the striatum. The $^{18}$F-labeled radiopharmaceutical washed out quickly from most of the brain regions, or 20 min after injection. The principle of tracer kinetic modelling was used to assess the cerebral microvasculature, so called perfusion imaging. This quantitative uptake was higher than the normal brain tissue and tended to be at lower volume. The degradation and remodelling of extracellular matrix macromolecules led to the loss of blood-brain barrier (BBB) integrity [22]. In the late phase (after 60 min), no definite uptake or retention of radioactive tracer activity was noted in the brain, except for blood-pool activity in the internal carotid artery. Thus, the contrast enhancement was suitable for diagnosis (figures 8(b)–(d)).

The optimized uptake time data were compared to those by Hsiao et al, of which a prominent uptake occurred at 60 min after injection [23]. Whilst, Lockhart et al confirmed 40–60 min to be an optimal time window for SUVR analysis of THK5351 PET data [14]. These results indicated that the optimized uptake time was 40–60 min could be the optimal uptake time for the normal brain and close to the results by Hsiao et al and Lockhart. However, the data were varied due to the differences of brain characteristics among population

| Region                      | Brain position (x, y, z) |
|-----------------------------|-------------------------|
| Anterior commissure (set origin) | (0, 0, 0)               |
| Frontal cortex              | (85, 92, 48)            |
| Fusiform gyrus              | (97, 74, 30)            |
| Inferior temporal cortex    | (80, 67, 16)            |
| Lingual gyrus               | (82, 88, 33)            |
| Middle temporal gyrus       | (70, 76, 35)            |
| Occipital cortex            | (82, 81, 21)            |
| Parahippocampal gyrus       | (92, 78, 30)            |
| Parietal cortex             | (82, 65, 58)            |
| Posterior cingulate         | (85, 93, 47)            |
| Precuneus                   | (82, 88, 59)            |
in each region of the world. The criteria to select the optimal uptake time of $^{18}$F-THK5351 was the amount of radiopharmaceuticals in an average impulse response of 10 regions in a macro-area related to the target binding of the brain. The data could be confirmed by the contrast enhancement in figure 8.

**Figure 6.** Graphs showing impulse response of $^{18}$F-THK5351 for 10 regions obtained by MATLAB processing. Interval times 1, 2, 3, and 4 denote 0–20, 20–40, 40–60, and 60–80 min, respectively.
4. Conclusion

The optimized uptake time of $^{18}$F-THK5351 PET/CT in the brain of normal Thai population can be investigated by the graphs of relationship between the radiopharmaceutical uptake quantity and the interval time. The graphs yields the optimized uptake time at an interval time of 3, i.e., 40–60 min.
Acknowledgments

We would like to thank Chulabhorn Hospital, Chulabhorn Royal Academy and King Mongkut’s Institute of Technology Ladkrabang for the funding support towards the accomplishment of this study. We also sincerely convey our special thanks to University of Tohoku, Sendai, Japan, for the provision of THK precursor in this study. Finally, we specially thank Prof Eyal Mishani, PhD, Director of Cyclotron / Radiochemistry Unit, Department of Nuclear Medicine, Hadassah Medical Center, Israel, as the visiting professor and consultant for our radiotracer production at National Cyclotron and PET Center, Bangkok, Thailand. This paper was based in part on the paper titled ‘The optimized uptake time of $^{18}$F-THK5351 PET/CT in normal Thai population,’ Proc. SPIE 10685, Biophotonics: Photonic Solutions for Better Health Care VI, 106852 A (2018) [doi:10.1117/12.2303399].

Disclosures

The study was approved by Chulabhorn Institutional Review Board and the written informed consent was obtained from all subjects (Project code: 050/2560). There was no financial conflict of interest. The authors had no relevant financial interest in this article and no potential conflicts of interest to declare.

ORCID iDs

Pachara Thonglim © https://orcid.org/0000-0002-0511-0597

References

[1] Arriagada P V et al 1992 Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer’s disease Neurology. 42 631–9
[2] Alonso A et al 2001 Hyperphosphorylation induces self-assembly of tau into tangles of paired helical filaments / straight filaments Proc. Natl Acad. Sci. USA 98 6923–8
[3] Braak H and Braak E 1994 Neuropathological stageing of Alzheimer-related changes Acta Neuropathol. (Berl). 82 239–59
[4] Braak E, Braak H and Mandelkow E M 1994 A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads Acta Neuropathol. (Berl). 87 554–67
[5] Braak H et al 2006 Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry Acta Neuropathol. (Berl). 112 389–404
[6] Delacourte A et al 1999 The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer’s disease Neurology 52 1158–65
[7] Guillozet L A, Weintraub S, Mash S D and Mesulam M M 2003 Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment Arch. Neurol. 60 729–36
[8] Thompson P W et al 2009 Interaction of the amyloid imaging tracer FDDNP with hallmark Alzheimer’s disease pathologies J. Neurochem. 109 623–30
[9] Chien D T et al 2014 Early clinical PET imaging results with the novel PHF-tau radioligand [F18]-T808 J. Alzheimers Dis. 38 171–84
[10] Villemagne V L et al 2014 In vivo evaluation of a novel tau imaging tracer for Alzheimer’s disease Eur. J. Nucl. Med. Mol. Imaging 41 816–26
[11] Bethauser T J et al 2017 In vivo comparison of tau radioligands $^{18}$F-THK-5351 and $^{18}$F-THK-5317 J. Nucl. Med. 58 996–1002
[12] Harada R et al 2015 $^{18}$F[THK-5317 PET for assessing neurofibrillary pathology in Alzheimer’s disease Eur. J. Nucl. Med. Mol. Imaging 42 1052–61
[13] Wilcock K G and Esiri M M 1982 Plaques, tangles and dementia: a quantitative study J. Neurol. Sci. 56 343–56
[14] Lockhart S N et al 2016 Dynamic PET measures of tau accumulation in cognitively normal older adults and Alzheimer’s disease patients measured using $^{18}$F[THK-5351 PLoS One 11 e0158460
[15] Blau M, Ganatra R and Bender M 1972 $^{18}$F-fluoride for bone imaging Semin. Nucl. Med. 2 31–7
[16] Klempt E, Battly C and Richard M J 2005 The antinucleon–nucleon interaction at low energy: annihilation dynamics Phys. Rep. 413 197–317
[17] Chen B et al 1992 Neutron yields and angular distributions produced in antiproton annihilation at rest in uranium Phys. Rev. C. Nucl. Phys. 45 2322–7
[18] Grant D F et al 2007 Skeletal PET with $^{18}$F-fluoride: applying new technology to an old tracer J. Nucl. Med. 49 68–78
[19] Thonglim P et al 2018 The optimized time of $^{18}$F-THK5351 PET/CT in normal Thai population Proc SPIE 10685 Biophotonics: Photonic Solutions for Better Health Care VI
[20] Villemagne V L and Okamura N 2016 Tau imaging in the study of aging, Alzheimer’s disease and other neurodegenerative conditions Curr. Opin. Neurobiol. 36 43–51
[21] Okamura N et al 2016 Advances in the development of tau PET radiotracers and their clinical applications Ageing Res. Rev. 30 107–13
[22] Rosen R B et al 1990 Perfusion imaging with NMR contrast agents Magn. Reson. Med. 14 249–65
[23] Hsiao I-T et al 2017 Biodistribution and radiation dosimetry for the tau tracer $^{18}$F-THK-5351 in healthy human subjects J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 58 1498–503