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ORIGINAL ARTICLE

# Phase I clinical study with different doses of $^{99m}$Tc-TRODAT-1 in healthy adults

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## Abstract

**Objectives** To study the pharmacokinetics, biodistribution, and injection doses of $^{99m}$Tc-TRODAT-1 in healthy adults.

**Methods** Thirty healthy individuals comprising 15 females and 15 males were randomly divided into three groups and the injection doses of $^{99m}$Tc-TRODAT-1 of group 1, 2, and 3 were 370 MBq, 740 MBq, and 1110 MBq, respectively. Assessments of subjective symptoms and tests were performed before and after injection. Blood and urine collections and whole-body planar imaging were analyzed at various time points. Bilateral brain striatal SPECT images obtained at 3.5 h PI were assessed visually and semiquantitatively.

**Results** No serious adverse events or deaths were observed in our study. The pharmacokinetic analysis showed that $^{99m}$Tc-TRODAT-1 was eliminated rapidly from the circulation, with just about 4% of the injected dose remaining in blood at 1 h post-injection. The mean cumulative urinary excretion over 24 h was just $2.96 \pm 0.96$%ID. The time-activity curve demonstrated that the radioactivity was mainly in liver and abdomen. The highest absorbed dose was in the dose-limiting organ, liver ($20.88 \pm 4.45 \times 10^{-3}$ mSv/MBq). The average effective dose was $5.22 \pm 1.05 \times 10^{-3}$ mSv/MBq. The clarity of striatal images assessed visually in group 1 was worse than that in group 2 and 3. The semiquantitative analysis showed that there were no differences in striatum/cerebellum between the three groups (group 1: $1.77 \pm 0.11$, group 2: $1.62 \pm 0.14$, and group 3: $1.75 \pm 0.20$; $P = 0.088$).

**Conclusions** $^{99m}$Tc-TRODAT-1 was safe to use in humans and showed the status of dopaminergic neurons specifically and clearly. The injection dose we suggested was 740 MBq.

**Keywords** $^{99m}$Tc-TRODAT-1 · Dopamine transporter · SPECT · Phase I · Pharmacokinetic analysis

## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder which affects predominately dopaminergic neurons in the substantia nigra pars compacta. Dopamine deficiency in the basal ganglia leads to an insidious onset of motor symptoms [1]. At present, the diagnosis of Parkinson's disease is still based on the presence of parkinsonian motor features. But if the diagnosis depends solely on clinical criteria, the rate of misdiagnosis is high [2]. So, in addition to clinical criteria, other diagnostic methods need to be used to improve the diagnostic accuracy.

Dopamine transporter (DAT), located on the plasma membrane of dopaminergic nerve terminals, plays a critical role in terminating dopamine neurotransmission and in maintaining dopamine homeostasis in the central nervous system by transporting synaptic dopamine into neurons [3]. DAT is thought to be a marker of

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dopamine (DA). Based on DAT as a marker, many radiopharmaceuticals like [$^{99m}$Tc]2β[*N*,*N*′-bis(2-mercaptoethyl) ethylenediaminomethyl]-3β-(4-chlorophenyl) tropane ($^{99m}$Tc-TRODAT-1), 2β-carbo methoxy-3β-(4-iodophenyl) tropane ($^{123}$I-β-CIT), and *N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodo-phenyl) nortropane ($^{18}$F-FP-CIT) have been developed to diagnose Parkinson's disease [4–6]. Among them, $^{99m}$Tc is much cheaper than $^{18}$F, $^{123}$I and other radionuclides and can be easily supplied by a $^{99}$Mo/$^{99m}$Tc generator. $^{99m}$Tc-labeled TRODAT-1 has high lipid solubility which can pass through the blood–brain barrier, enter the central nervous system and specifically bind to DAT in the presynaptic membrane of dopaminergic neurons [7]. Series of studies have indicated that using $^{99m}$Tc-TRODAT-1, single-photon emission computed tomography (SPECT) can demonstrate the density and distribution of DAT in the brain which can show changes in dopaminergic neurons and be used for diagnosing PD [4, 8–10]. In our phase 2 study, we assessed the sensitivity (98.96%) and specificity (94.12%) of $^{99m}$Tc-TRODAT-1 SPECT in diagnosing PD. The results showed that $^{99m}$Tc-TRODAT-1 could specifically bind to dopamine transporter and could be used to diagnose PD [11]. Except for diagnosing Parkinson's disease including early diagnosis, $^{99m}$Tc-TRODAT-1 can also be used for differentiating vascular parkinsonism, essential tremor, and parkinsonian syndromes from Parkinson's disease [10, 12, 13]. Studies have demonstrated the absence of adverse effects of $^{99m}$Tc-TRODAT-1 in animals and humans [9, 14, 15], indicating that $^{99m}$Tc-TRODAT-1 is clinically safe. Because there have been no clinical studies of $^{99m}$Tc-TRODAT-1 in healthy subjects in China, we undertook this phase I study in 30 healthy Chinese subjects to study the pharmacokinetics, biodistribution, and injection doses of $^{99m}$Tc-TRODAT-1 in this population.

## Materials and methods

This study was approved by the China Food and Drug Administration (Approval number: 2007L03822) and the ethics committee of Huashan Hospital Affiliated to Fudan University. All procedures performed in this study were in accordance with the guidelines of "Good Clinical Practice (GCP)" and with the principles of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was signed by healthy subjects who were informed of all aspects of the study and agreed to participate in this trial voluntarily.

### Subjects

After medical examination, physical examination, electrocardiogram, and laboratory tests, 30 healthy individuals (15 females and 15 males) were eligible and enrolled in this study from June 2009 to February 2010.

The inclusion criteria were as follows: healthy persons aged 19–45 years; ratio of males and females 1:1; range of body mass index (BMI) 19–25; the examinations which included neurological examination, physical examination, electrocardiogram, liver function, renal function, blood routine examination, and urine routine examination were normal or if abnormal had no clinical significance. The exclusion criteria were as follows: women in gestational and lactational period; mental or physical disability; inadequate hepatic or renal functions; past and present history of drug or alcohol abuse; history of hypersensitivity to drugs or food; use of drugs present because of disease; having received any other drug clinical trial within 3 months; having received any other radionuclide imaging within 14 days.

### Radiopharmaceutical

The dose of TRODAT-1 for every individual was 50 μg. $^{99m}$Tc-TRODAT-1 was synthesized as we previously reported [14]. The radiochemical purity was greater than 90% as determined by high-performance liquid chromatography (HPLC). Thirty subjects were divided randomly into three groups. Each group included five males and five females. The injection doses of $^{99m}$Tc-TRODAT-1 in group 1, 2, and 3 were about 370 MBq (10 mCi), 740 MBq (20 mCi), and 1110 MBq (30 mCi), respectively.

### Safety assessment

The inclusion and exclusion criteria were assessed again at the day before injection. Neurological examination and vital signs including blood pressure, pulse rate, and respiratory rate were measured before injection and at 30 min, 2 h, and 24 h post-injection (PI). The physical examination, 12-lead electrocardiogram, hematological test, biochemical test, and urinary test were conducted before injection and at 24 h PI.

### Pharmacokinetics, distribution and radiation dosimetry analysis

The blood samples were collected from the elbow vein in the contralateral side of the injection sites at 2 min, 5 min, 10 min, 20 min, 30 min, 1 h, 2 h, 4 h, 6 h, and 24 h PI, and urine samples were collected at 0–2 h, 2–4 h, 4–6 h, 6–12 h, and 12–24 h. The radioactivity in the blood and urine was counted to calculate a percentage of the injected dose (%ID). Pharmacokinetic analysis was performed by DAS version 2.1 software based on Akaike information criterion (AIC).

Anterior and posterior whole-body scanning was performed using SPECT at 5 min, 30 min, 1 h, 2 h, 4 h, 6 h, and 24 h PI. Regions of interests (ROIs) were drawn

around the brain, thyroid, heart, lung, abdomen, liver, spleen, and kidneys shown in ESM_1. The percentage of the injected dose in each organ at each point was analyzed.

Based on the pharmacokinetic results, the radiation dosimetry including absorbed and effective doses was calculated using OLINDA/EXM version 1.1 software according to the MIRD method for internal dose assessment. The radiation-absorbed doses of the main organs were assessed according to the file of 2007 Recommendations of the International Commission on Radiological Protection (ICRP103, 2007).

### Striatal imaging analysis

The brain SPECT was performed at 3.5 h after injection and evaluated both visually and semiquantitatively. The brain images were acquired in a 128 × 128 matrix through 360° rotation (180° for each head) using high-resolution fan beam collimators of Siemens NME.CAM Gantry Dual-Head Ex. Base (Siemens, German) and reconstructed using a ramp-Butterworth filter. The acquisition parameters and reconstruction method were all the same among the three groups. The results were described as "clear, less clear, and unclear." "Clear" means the SPECT images of the bilateral striatum including caudate nucleus and lentiform nucleus were very clear. "Unclear" means the images of the bilateral caudate nucleus and lentiform nucleus were all unclear. The resolution of the striatum images was considered "less clear" when it was between "clear" and "unclear." Two physicians independently analyzed the striatal imaging visually. For semiquantitative analysis, one transverse image containing the most intense activity in the striatal area was analyzed. The ROIs of the bilateral striatum (ST) and cerebellum (CB) were drawn like in our previous paper [11]. The ROI of bilateral striatum was drawn on the slice with the highest activity as shown in Fig. 3. The cerebellum area was used as the background. The ratio of regional brain uptakes of striatum/cerebellum (ST/CB) was calculated. One-way analysis of variance (ANOVA) was used to analyze the differences in ST/CB among the three groups.

## Results

### Characteristics of the subjects

The characteristics of the subjects in the three groups are shown in Table 1. The average age, height, weight, and BMI were 33.0 ± 7.4 year, 164.0 ± 8.9 cm, 60.7 ± 9.1 kg, and 22.5 ± 1.9 kg/m$^2$, respectively. The injection doses of the three groups were 400.8 ± 35.9 MBq (10.8 ± 1.0 mCi), 711.1 ± 64.0 MBq (19.2 ± 1.7 mCi), and 1032.3 ± 98.0 MBq (27.9 ± 2.6 mCi), respectively.

### Safety assessment

No serious adverse events or deaths were observed. The vital signs included blood pressure, pulse rate, and respiratory rate were normal in every subject before and after injection (ESM_2). The data of 12-lead electrocardiogram before and after injection showed that the electrocardiogram of all subjects was normal.

Four subjects showed abnormal laboratory tests as shown in Table 2. In group 1, NO. 9 has throat pain and increased white blood cell count, neutrophil percentage, and decreased lymphocyte percentage. The urine tests were abnormal in NO. 11 who has repeated urinary tract infections. No. 34 has increased neutrophil percentage, decreased red blood cell count, hemoglobin, and hematocrit. In group 3, No. 42 has increased lymphocyte percentage, decreased white blood cell count and neutrophil percentage. All laboratory tests of the 30 subjects before injection and 24 h PI were shown in ESM_3.

### Pharmacokinetic analysis

The change of radioactivity over time in blood is shown in Fig. 1a. $^{99m}$Tc-TRODAT-1 was eliminated rapidly from circulation, with just about 4% of injected dose remaining in blood at 1 h PI. According to Akaike information criterion, the metabolic process of $^{99m}$Tc-TRODAT-1 was fitted to the three-compartment model. The pharmacokinetic parameter of 30 subjects showed that the mean residence time ($MRT_{0-\infty}$), area under the curve ($AUC_{0-\infty}$), plasma elimination half-life ($t_{1/2}$), peak plasma radioactivity ($C_{max}$), and

**Table 1** Characteristics of subjects

| Group | Age (year) | Height (cm) | Weight (kg) | BMI (kg/m$^2$) | Injection dose (MBq) |
|---|---|---|---|---|---|
| 1 | 31.0 ± 7.5 | 166.0 ± 9.7 | 60.9 ± 10.7 | 22.1 ± 2.2 | 400.8 ± 35.9 (10.8 ± 1.0 mCi) |
| 2 | 36.1 ± 6.6 | 163.3 ± 8.2 | 62.0 ± 5.5 | 23.3 ± 1.4 | 711.1 ± 64.0 (19.2 ± 1.7 mCi) |
| 3 | 31.8 ± 6.9 | 162.6 ± 8.4 | 59.0 ± 9.9 | 22.1 ± 1.9 | 1032.3 ± 98.0 (27.9 ± 2.6 mCi) |
| Total | 33.0 ± 7.4 | 164.0 ± 8.9 | 60.7 ± 9.1 | 22.5 ± 1.9 | 715.3 ± 266.6 (19.3 ± 7.2 mCi) |

*BMI* body mass index

**Table 2** Adverse events of subjects at 24 h PI

| Group | Number | Parameter | Before injection | After injection | Normal range | Injection doses (MBq) |
|---|---|---|---|---|---|---|
| 1 | 9 | WBC ($\times 10^9$/L) | 5.81 | 15.70 | 4.50–11 | 492.1 (13.3 mCi) |
| | | Lymphocyte percentage (%) | 34.30 | 11.50 | 20–45 | |
| | | Neutrophil percentage (%) | 56.8 | 82.3 | 45–70 | |
| | 11 | Urine ketone | − | +++ | − | 388.5 (10.5 mCi) |
| | | Urine protein | − | trace | − | |
| | | Urine occult blood | + | ++ | − | |
| | 34 | Neutrophil percentage (%) | 64.7 | 79.9 | 45–70 | 384.8 (10.4 mCi) |
| | | Hemoglobin (g/L) | 127 | 97 | 110–160 | |
| | | Hematocrit (%) | 41.2 | 30.0 | 36–53 | |
| | | RBC ($\times 10^{12}$/L) | 5.75 | 3.33 | 3.5–5.5 | |
| 3 | 42 | WBC ($\times 10^9$/L) | 5.05 | 3.30 | 4.50–11 | 1047.1 (28.3 mCi) |
| | | Lymphocyte percentage (%) | 38 | 52.7 | 20–45 | |
| | | Neutrophil percentage (%) | 53.3 | 34.9 | 45–70 | |

*PI* post-injection, *WBC* white blood cells, *RBC* red blood cells

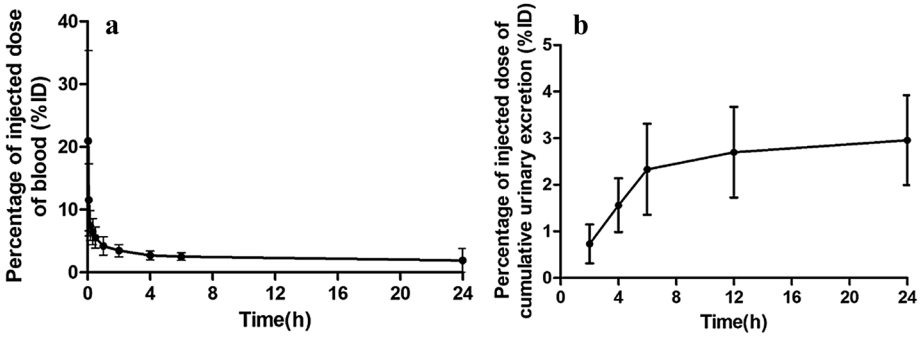


**Fig. 1** Time-activity curve of $^{99m}$Tc-TRODAT-1 in blood and urine. **a** The time-activity curve in blood. The activity in blood at 1 h was just 4%ID; **b** the time-activity curve in urine. The average cumulative urinary excretion over 24 h PI was 2.96 ± 0.96%ID. The data are expressed as mean ± SD

plasma clearance ($CL_Z$) were $1.52\times10^3\pm8.94\times10^2$ min, $6.31\times10^3\pm4.14\times10^3$%ID × min, $1.08\times10^3\pm6.54\times10^2$ min, 21.0 ± 14.3%ID, and 0.02 ± 0.009 $min^{-1}$.

The time-activity curve of cumulative urinary excretion over 24 h is shown in Fig. 1b. The mean cumulative urinary excretion over 24 h for all subjects was 2.96 ± 0.96%ID. The pharmacokinetic parameters of 30 subjects showed that the urine elimination half-life ($t_{1/2}$), elimination-rate constant (ke), and total urine output were 17.86 ± 18.97 h, 0.07 ± 0.05 $h^{-1}$, and 8.16 ± 2.44%ID, respectively.

## Whole-body distribution of $^{99m}$Tc-TRODAT-1

The whole-body planar images and time-activity curves acquired at different time points after injection are shown in Fig. 2a, b. The time-activity curve showed that the highest radioactivity at 5 min was found in liver (14.41 ± 2.33%ID), followed by abdomen (9.57 ± 2.43%ID) and lung (7.34 ± 2.04%ID). The highest radioactivity at 24 h was also in abdomen and liver (18.53 ± 9.22%ID and 18.31 ± 3.41%ID). The radioactivity of the other organs was all below 2%ID. The radioactivity in liver and abdomen increased slowly after injection, reached a peak at 6 h PI, and then decreased slowly.

## Radiation dosimetry

The average absorbed doses (mSv/MBq) in the target organs of the three groups are shown in Table 3. The liver showed the highest absorbed dose ($20.88\pm4.45\times10^{-3}$ mSv/MBq), followed by the spleen ($11.39\pm3.14\times10^{-3}$ mSv/MBq) and kidneys ($10.38\pm2.61\times10^{-3}$ mSv/MBq). The average effective dose equivalent and average effective dose were $6.65\pm1.32\times10^{-3}$ mSv/MBq and $5.22\pm1.05\times10^{-3}$ mSv/MBq, respectively.

## Striatal images

The striatal SPECT images of the three groups are shown in Fig. 3. The striatum including the caudate nucleus and lentiform nucleus was clear demonstrating that $^{99m}$Tc-TRODAT-1 binds to DAT specifically in the striatum. In Table 4, two "unclear" and one "less clear" were shown in group 1. Two "less clear" and one "less clear" were shown

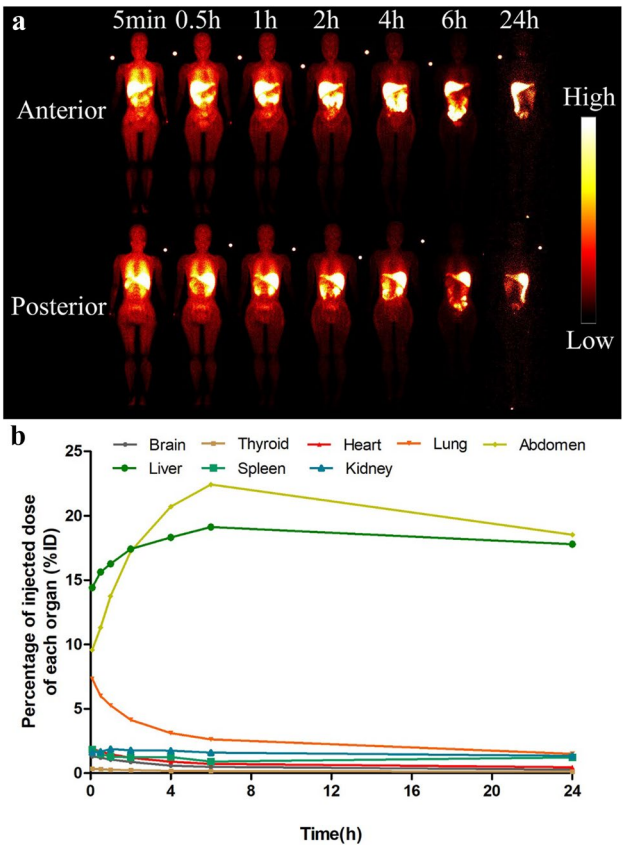


**Fig. 2** Whole-body planar images and time-activity curve in organs at various time points. **a** Whole-body planar image was performed at 5 min, 0.5 h, 1 h, 2 h, 4 h, 6 h, and 24 h PI; **b** percentage of injected dose (%ID) in organs over time. The highest radioactivity at 5 min PI was found in liver, followed by intestine and lung

in group 2 and group 3, respectively. The values of ST/CB in group 1, group 2, group 3, and total were 1.77 ± 0.11, 1.62 ± 0.14, 1.75 ± 0.20, and 1.71 ± 0.16, respectively, as shown in Table 4. One-way ANOVA showed no significant differences between or within the three groups ($P = 0.088$, ESM_4).

## Discussion

After $^{99m}$Tc-TRODAT-1, $^{99m}$Tc-labeled tropane derivatives as dopamine transporter (reuptake site)-imaging agents were first synthesized in 1997 by Hank F. Kung [16], and many studies have been performed in animals, non-human primates and humans to evaluate the density and distribution of DAT [4, 14, 15, 17–19]. $^{99m}$Tc-TRODAT-1 scintigraphy has been shown to have a high sensitivity and specificity to measure the gradual loss of DAT in PD patients [20]. $^{99m}$Tc-TRODAT-1 has also been used to distinguish PD from essential tremor, vascular parkinsonism, and parkinsonian syndromes [10, 12, 13]. $^{99m}$Tc-TRODAT-1 may be a good diagnostic agent for clinical use. In other countries, phase I clinical studies of $^{99m}$Tc-TRODAT-1 have been performed to evaluate its safety, pharmacokinetics, and radiation dosimetry [15, 21]. But no such phase I clinical studies of $^{99m}$Tc-TRODAT-1 have yet been conducted in China. So, we undertook the present clinical trial to assess its safety, pharmacokinetics, distribution, radiation dosimetry, and injected doses in healthy Chinese subjects for the first time.

In our study, there were no serious adverse events or deaths. The blood pressure, pulse rate, and respiratory rate of all 30 subjects were within the respective normal ranges before and after injection. And the 12-lead electrocardiogram did not show any meaningful changes in any subjects. But four persons had the abnormal laboratory test results in group 1 and group 3. According to their chief complaint with number 9 having throat pain and number 11 repeated urinary tract infections, their abnormal laboratory tests were not considered to have any relationship with $^{99m}$Tc-TRODAT-1. Numbers 34 and 42 had no uncomfortable symptoms, and

**Table 3** Estimated radiation dosimetry of target organs (mSv/MBq)

| Organs | Estimated radiation dosimetry ($\times 10^{-3}$) | | | |
|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Total |
| Brain | 1.69 ± 0.42 | 1.64 ± 0.31 | 1.59 ± 0.54 | 1.64 ± 0.42 |
| Heart | 7.37 ± 1.66 | 7.41 ± 1.19 | 7.89 ± 2.12 | 7.56 ± 1.66 |
| Kidneys | 10.61 ± 2.94 | 10.74 ± 1.98 | 9.79 ± 2.95 | 10.38 ± 2.61 |
| Liver | 20.97 ± 4.87 | 20.65 ± 3.29 | 21.02 ± 5.40 | 20.88 ± 4.45 |
| Lung | 6.79 ± 1.79 | 7.01 ± 1.07 | 7.42 ± 2.00 | 7.07 ± 1.63 |
| Gonads | 3.16 ± 1.19 | 3.17 ± 1.11 | 3.05 ± 1.39 | 3.13 ± 1.19 |
| Red Marrow | 3.15 ± 0.61 | 3.18 ± 0.44 | 3.10 ± 0.85 | 3.15 ± 0.63 |
| Spleen | 11.43 ± 2.95 | 12.11 ± 2.91 | 10.63 ± 3.66 | 11.39 ± 3.14 |
| Bladder | 3.37 ± 0.75 | 3.40 ± 0.63 | 3.27 ± 1.04 | 3.35 ± 0.80 |
| Total body | 3.81 ± 0.78 | 3.83 ± 0.55 | 3.76 ± 1.04 | 3.8 ± 0.79 |
| Effective dose equivalent | 6.64 ± 1.41 | 6.73 ± 0.86 | 6.57 ± 1.69 | 6.65 ± 1.32 |
| Effective dose | 5.21 ± 1.10 | 5.28 ± 0.73 | 5.16 ± 1.35 | 5.22 ± 1.05 |

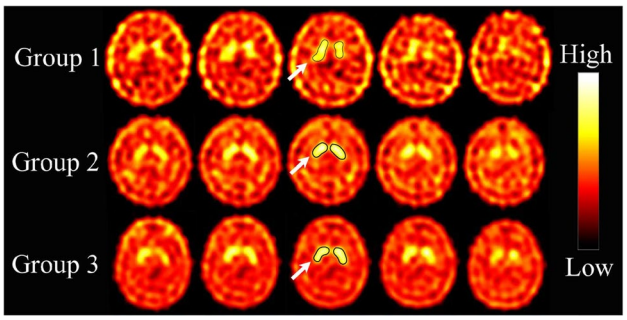


**Fig. 3** Striatal SPECT images of group 1, 2, and 3. Group 1,2, and 3 showed series of striatal images of subjects whose injection doses were 370 MBq (10 mCi), 720 MBq (20 mCi), and 1110 MBq (30 mCi), respectively. The white arrow showed the ROI of bilateral striatum on the slice with the highest activity in the three groups

they refused to repeat the blood tests, and so any relationship between the abnormal blood tests and radiotracer remained uncertain. In our phase II study including 34 healthy controls and 96 PD patients [11], only one showed an abnormal WBC level which was the same as our number 42, and no one showed abnormal RBC level. In another study, there were no meaningful changes in a complete blood cell count with differential performed 1, 4, and 24 h after the administration of the tracer [15]. So, whether the radiotracer induced an abnormal WBC level or not will need further study. Though the abnormal WBC level is not fatal, it reminds us to monitor the WBC level after injecting $^{99m}$Tc-TRODAT-1. In general, the radiotracer $^{99m}$Tc-TRODAT-1 is safe for use in humans in China.

$^{99m}$Tc-TRODAT-1 was quickly eliminated from blood with just about 4% of the injected dose remaining in blood at 1 h PI. The time-activity curve in blood in humans was

**Table 4** Evaluation of striatum images of 30 subjects visually and semiquantitatively

| Group | Number | Gender | Age (years) | Visually evaluation | ST/CB | Average (ST/CB) |
|---|---|---|---|---|---|---|
| 1 | 9 | Male | 28 | Unclear | 1.67 | 1.77 ± 0.11 |
| | 11 | Female | 37 | Clear | 1.68 | |
| | 15 | Female | 39 | Unclear | 1.74 | |
| | 23 | Male | 29 | Less clear | 1.68 | |
| | 25 | Male | 41 | Clear | 1.61 | |
| | 29 | Female | 41 | Clear | 1.79 | |
| | 33 | Male | 24 | Clear | 1.81 | |
| | 34 | Female | 23 | Clear | 1.97 | |
| | 35 | Female | 28 | Clear | 1.86 | |
| | 37 | Male | 20 | Clear | 1.85 | |
| 2 | 2 | Male | 39 | Clear | 1.56 | 1.62 ± 0.14 |
| | 10 | Female | 40 | Clear | 1.58 | |
| | 12 | Male | 31 | Clear | 1.68 | |
| | 13 | Female | 41 | Clear | 1.67 | |
| | 14 | Female | 42 | Clear | 1.67 | |
| | 17 | Female | 40 | Clear | 1.96 | |
| | 19 | Male | 36 | Less clear | 1.47 | |
| | 27 | Male | 43 | Clear | 1.49 | |
| | 36 | Male | 24 | Clear | 1.55 | |
| | 40 | Female | 25 | Less clear | 1.55 | |
| 3 | 3 | Male | 29 | Clear | 1.85 | 1.75 ± 0.20 |
| | 5 | Female | 44 | Clear | 1.55 | |
| | 6 | Female | 44 | Clear | 1.51 | |
| | 18 | Female | 28 | Clear | 1.71 | |
| | 22 | Male | 25 | Less clear | 1.56 | |
| | 24 | Male | 37 | Clear | 1.60 | |
| | 30 | Male | 25 | Clear | 1.83 | |
| | 38 | Male | 28 | Clear | 1.88 | |
| | 41 | Female | 27 | Clear | 1.80 | |
| | 42 | Female | 31 | Clear | 2.16 | |
| Total | | | 33.0 ± 7.4 | Clear | | 1.71 ± 0.16 |

*ST/CB* the ratio of regional brain uptakes of striatum and cerebellum

consistent with that in rabbits and baboons [14, 22]. The mean cumulative urinary excretion over 24 h for all subjects was just 2.96 ± 0.96%ID. From the whole-body distribution study, the highest radioactivity at various time points was in abdomen and liver. The highest radioactivity in kidney was just below 2%ID. These results showed that the radiotracer was excreted by the hepatobiliary system, the same in rats and humans [14, 15, 23].

The amount of $^{99m}$Tc-TRODAT-1 injected in our study was in three different doses [370 MBq (10 mCi), 740 MBq (20 mCi), and 1110 MBq (30 mCi)]. The organ absorbing the maximum radioactivity was liver, followed by spleen. The dose-limiting organ, liver, in three groups receives approximately 0.021 mSv/MBq which was less than in another study (0.047 mSv/MBq) [24].

The striatal images were evaluated visually and semiquantitatively. In group 1, two subjects showed unclear striatal images visually which were not found in group 2 or 3. These results demonstrated that the clarity of striatal images assessed visually in group 1 was worse than that in group 2 and 3. Through analyzing the data of striatal images semiquantitatively, there were no significant differences between different doses. The average value of ST/CB of 30 subjects in our study was 1.71 ± 0.16. In Ping Fang's study in which the injection doses were 555–740 MBq (15–20 mCi) and the mean age of healthy volunteers was 59.91 ± 17.06 years, the mean value of ST/CB was 1.51 ± 0.17 which was lower than our study [25]. In another study in which the mean age of the healthy subjects was 49.0 ± 14.1 years, the average value of ST/CB was also lower, namely 1.57 ± 0.17 for the right striatum and 1.61 ± 0.14 for the left striatum [the injection dose was 740 MBq (20 mCi)] [18]. But the average value was lower than in one study in which it was 1.98 ± 0.11. [the injection doses was 740–925 MBq (20–25 mCi)] [26]. In this study, the normal volunteers were younger than ours. Numerous studies had shown that dopamine transporter in striatum declined with increasing age [27–30]. So the differences of the value of ST/CB among the previous studies and the present study may due to age differences. In our study, the image clarity in subjects who received about 370 MBq (10 mCi) doses was worse than that with 740 MBq (20 mCi) and 1110 MBq (30 mCi). The images in subjects with doses of 740 MBq (20 mCi) and 1110 MBq (30 mCi) were better for doctors to evaluate the status of dopaminergic neurons in PD patients and other neurodegenerative disorders. But increasing the injection activity is obviously associated with more radioactivity. The internal organs will receive more radioactivity. One other study suggested that the minimum amount of 740 MBq (20 mCi) should be used according to the concept of as low as reasonably achievable (ALARA) for radiation protection [24]. Compared with our study and other studies, we suggested that the injection dose of $^{99m}$Tc-TRODAT-1 in China is about 740 MBq (20 mCi).

## Conclusions

In our study, $^{99m}$Tc-TRODAT-1 was found to be safe for human use. The pharmacokinetic and biodistribution analysis showed that this radiotracer was quickly eliminated from blood and excreted by the hepatobiliary system. Through evaluating the striatal images visually and semiquantitatively, $^{99m}$Tc-TRODAT-1 brain SPECT can show the status of dopaminergic neurons specifically and clearly, and the injection dose we suggested was about 740 MBq (20 mCi).

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

## References

1. Kalia LV, Lang AE. Parkinson's disease. The Lancet. 2015;386(9996):896–912.
2. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55(3):181–4.
3. Chen N, Reith ME. Structure and function of the dopamine transporter. Eur J Pharmacol. 2000;405(1–3):329–39.
4. Mozley PD, Schneider JS, Acton PD, Plossl K, Stern MB, Siderowf A, et al. Binding of [99mTc]TRODAT-1 to dopamine transporters in patients with Parkinson's disease and in healthy volunteers. J Nucl Med. 2000;41(4):584–9.
5. Staffen W, Mair A, Unterrainer J, Trinka E, Ladurner G. Measuring the progression of idiopathic Parkinson's disease with [123I] beta-CIT SPECT. J Neural Transm (Vienna). 2000;107(5):543–52.
6. Wang J, Zuo CT, Jiang YP, Guan YH, Chen ZP, Xiang JD, et al. 18F-FP-CIT PET imaging and SPM analysis of dopamine transporters in Parkinson's disease in various Hoehn & Yahr stages. J Neurol. 2007;254(2):185–90.
7. Kung HF, Kim HJ, Kung MP, Meegalla SK, Plossl K, Lee HK. Imaging of dopamine transporters in humans with technetium-99m TRODAT-1. Eur J Nucl Med. 1996;23(11):1527–30.
8. Chou KL, Hurtig HI, Stern MB, Colcher A, Ravina B, Newberg A, et al. Diagnostic accuracy of [99mTc]TRODAT-1 SPECT imaging in early Parkinson's disease. Parkinsonism Relat Disord. 2004;10(6):375–9.
9. Huang WS, Lin SZ, Lin JC, Wey SP, Ting G, Liu RS. Evaluation of early-stage Parkinson's disease with 99mTc-TRODAT-1 imaging. J Nucl Med. 2001;42(9):1303–8.
10. Tzen KY, Lu CS, Yen TC, Wey SP, Ting G. Differential diagnosis of Parkinson's disease and vascular parkinsonism by (99m)Tc-TRODAT-1. J Nucl Med. 2001;42(3):408–13.
11. Sun Y, Liu CJ, Zp Chen, Li B, Lv ZW, Lou JJ, et al. A phase 2, open-label, multi-center study to evaluate the efficacy and safety of Tc-TRODAT-1 SPECT to detect Parkinson's disease. Ann Nucl Med. 2019. https://doi.org/10.1007/s12149-019-01412-2.
12. Fallahi B, Esmaeili A, Beiki D, Oveisgharan S, Noorollahi-Moghaddam H, Erfani M, et al. Evaluation of (99m)

Tc-TRODAT-1 SPECT in the diagnosis of Parkinson's disease versus other progressive movement disorders. Ann Nucl Med. 2016;30(2):153–62.
13. Wang J, Jiang YP, Liu XD, Chen ZP, Yang LQ, Liu CJ, et al. 99mTc-TRODAT-1 SPECT study in early Parkinson's disease and essential tremor. Acta Neurol Scand. 2005;112(6):380–5.
14. Fang P, Wu CY, Liu ZG, Wan WX, Wang TS, Chen SD, et al. The preclinical pharmacologic study of dopamine transporter imaging agent [99mTc]TRODAT-1. Nucl Med Biol. 2000;27(1):69–75.
15. Mozley PD, Stubbs JB, Plossl K, Dresel SH, Barraclough ED, Alavi A, et al. Biodistribution and dosimetry of TRODAT-1: a technetium-99m tropane for imaging dopamine transporters. J Nucl Med. 1998;39(12):2069–76.
16. Meegalla SK, Plossl K, Kung MP, Chumpradit S, Stevenson DA, Kushner SA, et al. Synthesis and characterization of technetium-99m-labeled tropanes as dopamine transporter-imaging agents. J Med Chem. 1997;40(1):9–17.
17. Dresel SH, Kung MP, Huang X, Plossl K, Hou C, Shiue CY, et al. In vivo imaging of serotonin transporters with [99mTc]TRODAT-1 in nonhuman primates. Eur J Nucl Med. 1999;26(4):342–7.
18. Hu P, Chen L, Zhang HQ, Li JR, Liang H. Single photon emission computer tomography of dopamine transporters in monkeys and humans with 99mTc-TRODAT-1. Chin Med J Engl. 2004;117(7):1056–9.
19. Hwang JJ, Liao MH, Yen TC, Wey SP, Lin KJ, Pan WH, et al. Biodistribution study of [99mTc] TRODAT-1 alone or combined with other dopaminergic drugs in mice with macroautoradiography. Appl Radiat Isot. 2002;57(1):35–42.
20. Weng YH, Yen TC, Chen MC, Kao PF, Tzen KY, Chen RS, et al. Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. J Nucl Med. 2004;45(3):393–401.
21. Koch W, Pogarell O, Popperl G, Hornung J, Hamann C, Gildehaus FJ, et al. Extended studies of the striatal uptake of 99mTc-NC100697 in healthy volunteers. J Nucl Med. 2007;48(1):27–34.
22. Kushner SA, McElgin WT, Kung MP, Mozley PD, Plossl K, Meegalla SK, et al. Kinetic modeling of [99mTc]TRODAT-1: a dopamine transporter imaging agent. J Nucl Med. 1999;40(1):150–8.
23. Cleynhens BJ, de Groot TJ, Vanbilloen HP, Kieffer D, Mortelmans L, Bormans GM, et al. Technetium-99m labelled integrated tropane-BAT as a potential dopamine transporter tracer. Bioorg Med Chem. 2005;13(4):1053–8.
24. Huang CK, Wu J, Cheng KY, Pan LK. Optimization of imaging parameters for SPECT scans of [99mTc]TRODAT-1 using Taguchi analysis. PLoS ONE. 2015;10(3):e0113817.
25. Bao SY, Wu JC, Luo WF, Fang P, Liu ZL, Tang J. Imaging of dopamine transporters with technetium-99m TRODAT-1 and single photon emission computed tomography. J Neuroimaging. 2000;10(4):200–3.
26. Wang P, Hu P, Yue DC, Liang H, Xu JH. The clinical value of Tc-99m TRODAT-1 SPECT for evaluating disease severity in young patients with symptomatic and asymptomatic Wilson disease. Clin Nucl Med. 2007;32(11):844–9.
27. Varrone A, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Booij J, et al. European multicentre database of healthy controls for [123I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. Eur J Nucl Med Mol Imaging. 2013;40(2):213–27.
28. Mozley PD, Acton PD, Barraclough ED, Plossl K, Gur RC, Alavi A, et al. Effects of age on dopamine transporters in healthy humans. J Nucl Med. 1999;40(11):1812–7.
29. Volkow ND, Fowler JS, Wang GJ, Logan J, Schlyer D, MacGregor R, et al. Decreased dopamine transporters with age in health human subjects. Ann Neurol. 1994;36(2):237–9.
30. van Dyck CH, Seibyl JP, Malison RT, Laruelle M, Zoghbi SS, Baldwin RM, et al. Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. Am J Geriatr Psychiatry. 2002;10(1):36–43.