Pharmacokinetics and dosimetry of iodine-123 labelled PE2I in humans, a radioligand for dopamine transporter imaging

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Abstract. The iodine-123 labelled selective ligand *N*-(3-iodoprop-2*E*-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl)nortropane ([^{123}I]PE2I) was evaluated as a probe for in vivo dopamine transporter imaging in the human brain. Six healthy subjects were imaged with a high-resolution single-photon emission tomography scanner. Striatal radioactivity peaked at 1 h after injection. The background radioactivity was low. The volume of distribution in the striatum was 94±24 ml/ml. The results were compared with those of [^{123}I]β-CIT imaging. There was no significant uptake of [^{123}I]PE2I in serotonin-rich regions such as the midbrain, hypothalamus and anterior gingulus, suggesting that in vivo binding is specific for the dopamine transporter. One main polar metabolite of [^{123}I]PE2I was found in plasma, and the parent plasma concentration decayed rapidly. Radiation exposure to the study subject is 0.022±0.004 mSv/MBq (effective dose). The preliminary results suggest that [^{123}I]PE2I is a selective SPET ligand for imaging striatal dopamine transporter density.

Key words: Dopamine transporter – Human brain – Single-photon emission tomography – Striatum

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Introduction

Cocaine derivatives such as 2-β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) and its fluoroalkyl derivates such as β-CIT-FE and β-CIT-FP have high affinity for the dopamine transporter (DAT), and have been used for brain imaging with positron emission tomography (PET) [1] and with single-photon emission tomography (SPET) [2, 3]. Although these radioligands are sensitive for DAT imaging, they are not selective because of their affinity for other monoamine transporters. A new selective radioligand for dopamine transporter imaging, *N*-(3-iodoprop-2*E*-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl) nortropane ([^{125}I]PE2I), has been developed [4] and its binding to human post-mortem brain has been investigated [5]. It also showed high affinity for the DAT with a K_d of 0.09 n*M* [6]. Its inhibitory constants towards DA, 5-HT and NE transporters are 17 n*M*, 500 n*M* and >1000 n*M*, whereas those of β-CIT were 27 n*M*, 3 n*M* and 80 n*M*, respectively [4–6]. PE2I has also been labelled with carbon-11 and demonstrated a selective binding to the DAT in monkeys [7].

In the present communication we report our initial findings of SPET imaging, plasma kinetics and radiation dosimetry with iodine-123 labelled PE2I in the living human brain. The results are compared with those of [^{123}I]β-CIT imaging.

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Materials and methods

Study subjects. Five healthy males and one female (23–37 years) were studied. Informed consent was obtained and the nature of the studies was fully explained. The study was approved by the Ethical Committee of Kuopio University Hospital. The subjects were given 400 mg potassium perchlorate per os 1 h before the study and 200 mg at 12 and at 24 h after injection of the tracer in order to reduce ^{123}I uptake in the thyroid and in the salivary gland.

Chemistry. The radiolabelling of PE2I as well as β-CIT was performed by MAP Medical Technologies Oy (Tikkakoski, Finland). Iododestannylation of the precursor, *N*-(3-tributylstannylprop-2*E*-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl)nortropane was performed with carrier-free $Na^{123}I$ (CIS bio international, Gif-sur-Yvette, France) in minute volume in the presence of chloramine-T at pH 4.5. The product was purified with semipreparative high-performance liquid chromatography (HPLC) on μBondapak C18 column (Waters, Milford, Mass., USA) with ethanol and 0.01 *M* phosphoric acid (85/65). The radioactivity peak which equals the retention time of appropriate reference standard was collected.

The product was diluted with isotonic saline and phosphate buffer until the concentration of ethanol was <15% and sterilized by filtration through a 0.22-μm membrane. The radiochemical purity of products were checked before the injection with a HPLC system.

Determination of labelled metabolites. Venous blood samples were collected at 2, 5, 10, 30, 60, 120, 160 and 220 min after injection of the tracer. Plasma was separated and its radioactivity was measured. A gradient HPLC method was used for the determination of labelled metabolites in plasma [8]. Briefly, a Waters (Waters, Millford, Mass., USA) HPLC system with a radiomatic 150 TR radioisotope detector (Packard Instrument Company, Meriden, Conn., USA) followed by a Waters 484 UV-detector at 254 nm was used with μBondapak C18 column. The gradient HPLC programme used was a mixture of acetonitrile in phosphoric acid (0.01 *M*) with acetonitrile from 25% to 60% in 6 min, a 2-min hold at 60%, back to 25% in 1 min, and ending the run at 10 min.

SPET brain imaging. The radioactivity of [^{123}I]PE2I injected varied from 140 to 215 MBq (radionuclide purity ≥99.8%). The dose was administered into the antecubital vein in a dimly lit and quiet room. Dynamic SPET scans were performed using a Siemens MultiSPECT 3 gamma camera with fan-beam collimators (Siemens Medical Systems, Inc., Hoffman Estates, Ill., USA). The energy window (15%) was centered around the photopeak of ^{123}I. During a 360° rotation (120° per camera head), 40 views/head were acquired in a 128×128 matrix mode. The radius of rotation was 13.8 cm. The raw data were reconstructed with the filtered back-projection technique (Butterworth: order 8 and a cut-off frequency 0.75 cm^{-1}) and corrected using Chang's attenuation method with a uniform attenuation coefficient of 0.10 cm^{-1}. The imaging resolution was 7–8 mm. Cross-calibration between the plasma samples and the regional count densities was performed.

Whole-body imaging. The study subjects were scanned at 2, 4 and 7 h after injection of the tracer with a dual-headed Siemens E.CAM gamma camera with high-resolution collimators. A constant scanning speed of 20 cm/min was used in a 1024×256 matrix mode.

Data analysis. Transaxial slices were visually surveyed and two slices were conse-cutively summarized to the total slice thickness of 5.6 mm. Regions of interest were drawn onto the cerebellum, the white matter (= free + non-specific binding) and the striatum. Average regional counts were used in calculations, and time-activity curves were corrected for radioactivity decay of ^{123}I and printed out (Fig. 1).

The volume of distribution of [^{123}I]PE2I (V_D in ml/ml) after the bolus injection in the striatum was estimated as:

$$V_D = \text{area of ROI/plasma integral,} \quad (1)$$

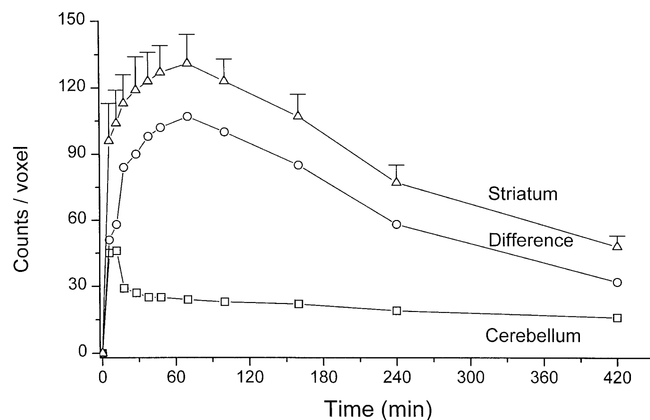

Fig. 1. Mean (*n*=6) regional time-activity curves of the [^{123}I]PE2I study in the striatum and cerebellum as well as their difference. The curves were normalized to the counts/voxel/ID/body weight. The *error bars* show one standard deviation of the striatal time-activity curve

where area of ROI is the integral of the striatal time-activity curve and the plasma integral is the corresponding integral of the parent plasma radioactivity.

A simple formula can be used to calculate the specific binding of [^{123}I]PE2I in the given region *i*:

$$\text{Specific binding of the striatum} = (\text{ROI} - \text{WM})/\text{ROI}, \quad (2)$$

where ROI=regional counts/voxel at the curve peak (T_P) and WM=white matter counts/voxel at T_p.

Regional radioactivities of the whole-body images were calculated over the following regions: brain, thyroid, lungs, liver, spleen, intestine tract, urinary bladder and the rest of the body. The square root of the anterior × posterior counts was used to calculate percentage activities of the given region (%/ID) by relating it to the square root of the whole body anterior × posterior counts at 2 h.

[^{123}I]β-CIT SPET. Four of the male subjects were administrated of 185 MBq of [^{123}I]β-CIT day after the [^{123}I]PE2I study. The scan was performed 24 h after injection with the same camera and computer settings as those used for the [^{123}I]PE2I study.

Results

Preparation of [^{123}I]PE2I

The product was found to be sterile at all times. The incorporation of ^{123}I to form [^{123}I]PE2I was 90%–98%. The overall yield was 70%–85% with a radiochemical purity of >98%. The specific radioactivity was estimated to be 8.7 TBq/μmol.

Metabolites in plasma

One main radioactive polar metabolite was found. Minor amounts of other metabolites were also observed which were more polar than ^{123}IPE2I itself. The parent radioactivity decayed rapidly. The percentage of unchanged

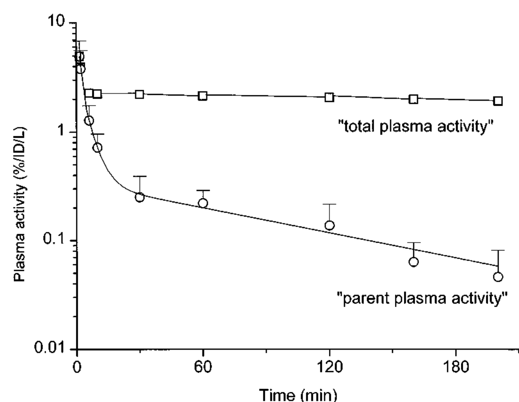

Fig. 2. A log/linear plot of the total plasma radioactivity and the unchanged [^{123}I]PE2I in plasma with time (n=6). The *error bars* show one standard deviation. A three-exponential function was fitted to the observed parent time-activity curve: $y(t)=0.107e^{-0.737t} + 0.033e^{-0.144t} + 0.0034e^{-0.006t}$

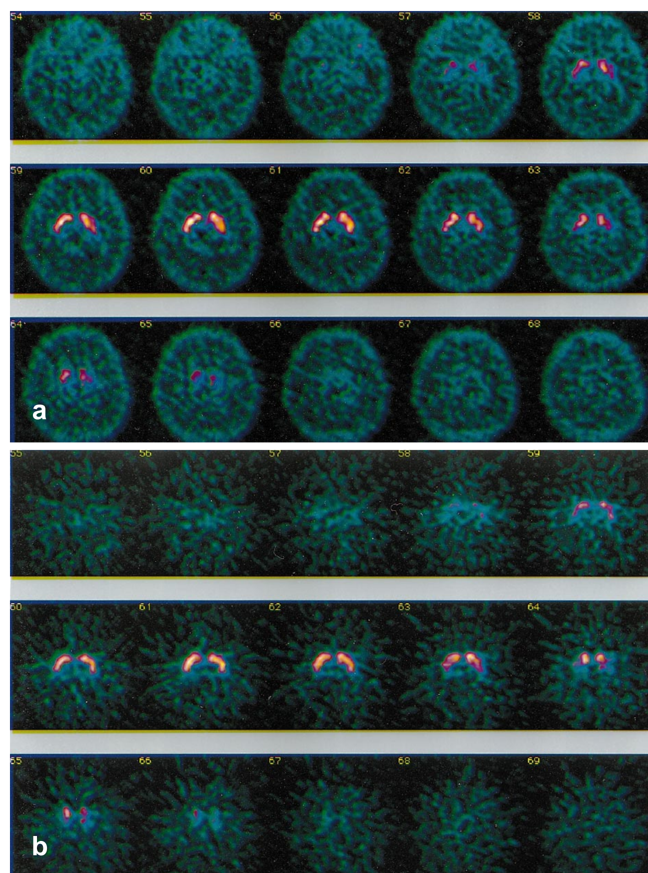

Fig. 3. A comparative display of transaxial slices of a brain scan in a healthy male 70 min after injection of 150 MBq of [^{123}I]PE2I (**a**) and 24 h after injection of 185 MBq of [^{123}I]β-CIT (**b**). Note that the background activity of [^{123}I]PE2I (**a**) is higher than that of [^{123}I]β-CIT (**b**) due to the different binding kinetics. There is high uptake in the scalp, suggesting that the parent radioligand dissolves to free iodine and metabolites

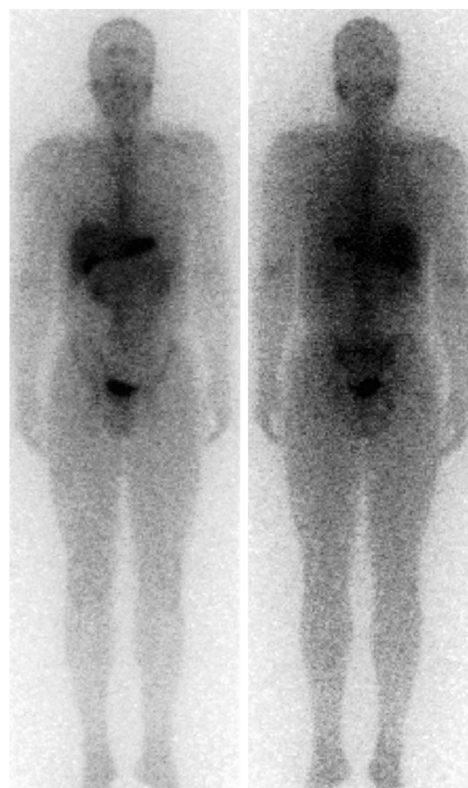

Fig. 4. Whole-body scan taken 2 h after injection of [^{123}I]PE2I shows relatively high radioactivity in the liver and the urinary bladder. There is no intense regional uptake in the lungs (serotonin-rich region) as found in [^{123}I]β-CIT scans

^{123}IPE2I was 13%±4% (mean ± standard deviation) and 7%±3% at 30 min and 120 min, respectively (Fig. 2).

SPET brain imaging

The highest specific uptake of [^{123}I]PE2I in the striatum was at 64–84 min after injection (Fig. 3). The biological half-life of the striatal washout of tracer was 4.7±0.5 h. The volume of distribution of [^{123}I]PE2I was 94±24 ml/ml, which was significantly less than that of [^{123}I]β-CIT (170±27 ml/ml). The striatal specific binding was 0.89±0.02 for [^{123}I]PE2I and 0.92±0.01 for [^{123}I]β-CIT.

Whole-body imaging

The most intense uptake was found in the urinary bladder, the liver and the intestinal tract (Fig. 4). The majority of radioactivity clears through the urinary tract. Washout time of the whole-body radioactivity was 9.5±0.6 h. The brain uptake was 3.1±0.3%/ID at 1 h after injection. The peak uptake in the striatum was slightly lower (0.34±0.03%/ID) than that of [^{123}I]β-CIT (0.40±0.03%/ID; P<0.01).

The highest radiation exposure is for the urinary bladder wall (0.07 mGy/MBq) and the estimated effective dose is 0.022±0.004 mSv/MBq (MIRDOSE 3, Oak Ridge National Laboratories, Oak Ridge, Tenn., USA). The effective dose was significantly less than that of [^{123}I]β-CIT (0.034±0.005 mSv/MBq).

Discussion

Previous animal studies have shown that DAT is mainly localized to the striatum [5, 9] and to a lesser extent the substantia nigra, but not other regions such as the midbrain, the hypothalamus and the anterior gingulus. The results of the present study confirm that [^{123}I]PE2I accumulates in the striatum and that no other brain regions show significant uptake, as found using other cocaine analogues [1–3, 7] and [^{123}I]IPT [10]. Moreover, β-CIT and its analogues have radioactive metabolites which may obstruct DAT quantitation [8]. [^{123}I]PE2I transforms rapidly to one main polar metabolite which is unlikely to enter brain tissue prior to the suggested scan time between 60 and 100 min.

There is increased interest in the development of technetium-99m-based radioligands, so bypassing the need for cyclotron-produced radionuclides for receptor imaging. Kung et al. [11] recently reported the initial results of the use of [^{99m}Tc]TRODAT-1 for DAT imaging. However, the relatively low brain uptake, the low striatum-to-background ratio (<2 vs 9 with [^{123}I]PE2I) and the poor imaging quality do not favour use of the present form of [^{99m}Tc]TRODAT-1 in clinical routine.

The volume of distribution of [^{123}I]PE2I was smaller than that of [^{123}I]β-CIT, mainly due to their different binding kinetics. However, the imaging and dosimetric properties of [^{123}I]PE2I favour its use in clinical practice. The striatum-to-background ratio is high and radiation exposure to patients is low.

SPET studies on brain imaging of DAT density have been performed using non-selective radioligands [2, 3, 10] which also have a relatively high accumulation in serotonin-rich regions such as lungs [3]. These tissues are an excellent sink for the first hours after injection, and then afterwards a source. Numerical indices such as specific binding are difficult to compare among the individual study subjects due to lack of the proper input function.

In conclusion, [^{123}I]PE2I appears to be a selective SPET ligand with low non-specific binding for imaging striatal DAT density. The scan time is optimal (60–100 min p.i.) in daily routine.

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