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Whole-body distribution and radiation dosimetry of [^{11}C]telmisartan as a biomarker for hepatic organic anion transporting polypeptide (OATP) 1B3

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ABSTRACT

Introduction: Telmisartan, a nonpeptide angiotensin II AT1 receptor antagonist used as an antihypertensive drug, is specifically taken up by the liver through the OATP1B3. PET imaging with [^{11}C]telmisartan is expected to provide information about the whole body pharmacokinetics of telmisartan as well as its transport property by OATP1B3. The purpose of the study was to determine the biodistribution and radiation dosimetry of [^{11}C]telmisartan in humans.
Methods: Biodistribution of [^{11}C]telmisartan was measured in three rats and six healthy male human volunteers. In the rat study, a dynamic emission scan was performed for 90 min. In the human study, dynamic whole-body PET images were acquired after intravenous injection of [^{11}C]telmisartan. ROIs were defined for source organs on the PET images to measure time-course of [^{11}C]telmisartan uptake as percentage injected dose and the number of disintegration for each organ. Radiation dosimetry was calculated with OLINDA/EXM.
Results: In the rat study, most radioactivity was rapidly taken up by the liver and part of it was excreted into the biliary tract and intestine. Extrapolating from the rat data, the effective dose for the adult human being was estimated to be 3.65±0.01 microSv/MBq (n=3). In the human study, most of the tracer was taken up by the liver as well, although not as rapidly as in the rat. The activity in the gall bladder and intestine increased gradually. The effective dose for the adult human being was 4.24±0.09 microSv/MBq (n=6).
Conclusions: [^{11}C]Telmisartan is a safe PET tracer with a dosimetry profile comparable to other common ^{11}C PET tracers.

1. Introduction

Telmisartan, an antihypertensive drug marketed as Micardis, inhibits vasoconstriction and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues. From the standpoint of pharmacokinetics, telmisartan is taken up by the liver, conjugated with glucuronic acid and subsequently excreted into bile as telmisartan glucuronide [1,2].

The pharmacokinetics of orally administered telmisartan is known to be nonlinear over the dose of 40 mg, with greater than proportional increases of plasma concentrations with increasing dose. According to the phase I clinical trial of telmisartan [3], following oral administration of 20 mg, 40 mg and 80 mg tablet on Japanese healthy adults, peak concentration (C_{max}) of telmisartan was 33.84±17.32 (n=31), 78.52±32.72 (n=29) and 365.81±253.08 ng/ml (n=30), and the area under the plasma concentration-time curve (AUC_{0-24h}) was 424.65±232.25 (n=31), 807.41±334.76 (n=29) and 2304.54±1522.85 ng*h/ml (n=30), respectively.

Telmisartan is specifically taken up by hepatocytes through organic anion transporting polypeptide (OATP) 1B3 [1]. OATP1B3 is expressed on the sinusoidal membrane of the hepatocytes, and is thought to be involved in the transport of a wide variety of drugs together with OATP1B1. Thus, OATP1B3 governs the hepatic clearance of telmisartan and saturation of OATP1B3-mediated uptake at high dose was considered to be one of the possible mechanisms for the non-linear pharmacokinetics of telmisartan. However, it was almost impossible to directly measure the transport of drugs from blood circulation to liver on humans because of difficulty in the measurement of tissue concentration of drugs.

PET is a powerful non-invasive technique in which drugs labeled with positron emitters are injected and the distribution and time course of radioactivity are imaged. The high sensitivity and exceptional spatial–temporal resolution of PET make it a particularly useful tool for estimating the in vivo function of drug transports in various tissues over time following intravenous administration of a

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radiolabeled drug. Very recently, Takashima et al. have demonstrated that [^{11}C]15*R*-TIC could be useful for the evaluation of transporter-mediated hepatic uptake and biliary excretion [4]. The preliminary data in a rat study using a small animal PET scanner as well as radiometric HPLC showed that administered radioactivity of [^{11}C]telmisartan was promptly taken up by the liver and its acylglucuronide was excreted into the bile, and that accumulation of radioactivity in the other organs was very low after intravenous administration of [^{11}C]telmisartan to the rats [5].

Therefore, PET imaging with [^{11}C]telmisartan is expected to provide information about the whole body pharmacokinetics of telmisartan as well as the transport function by hepatic OATP1B3 in humans. The changes in the transport function of OATP1B3 caused by drug–drug interaction, genetic polymorphisms and liver diseases may affect the hepatic clearance of OATP1B3 substrates, resulting in the changes in the plasma concentration and its pharmacological effect. For example, Kiyotani et al. demonstrated that genetic polymorphism of SLCO1B3 (rs11045585), which encodes OATP1B3, increased the risk of docetaxel-induced neutropenia possibly due to the decreased plasma concentration of docetaxel [6].

Because [^{11}C]telmisartan has never been administered in humans, the purpose of the present study was to confirm its safety and determine the biodistribution and radiation exposure by [^{11}C]telmisartan in healthy volunteers. Considering the species difference, dosimetry was estimated from the rat data before the first human subject was injected with [^{11}C]telmisartan, based on which practicability of estimating human dosimetry from rat data was also discussed. The liver kinetic analysis is presented in another paper.

2. Materials and methods

2.1. Radiopharmaceutical preparation

[^{11}C]Telmisartan was synthesized by ^{11}C-methylation of *N*-desmethyl telmisartan with [^{11}C]CH_3I followed by HPLC separation, and radiochemical purity of >97% was obtained [7]. Fig. 1 shows structure formula for [^{11}C]telmisartan.

2.2. Rat study

Male Sprague–Dawley (SD) rats weighing 240±3 g (n=3) were purchased from Japan SLC Inc. (Shizuoka, Japan). All experimental protocols were approved by the Ethics Committee on Animal Care and Use of the Center for Molecular Imaging Science in RIKEN, and were performed in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1985).

All PET scans were performed using a microPET Focus220 scanner (Siemens, Knoxville, TN) [8] designed for laboratory animals. PET experiments with [^{11}C]telmisartan were performed in male SD rats.

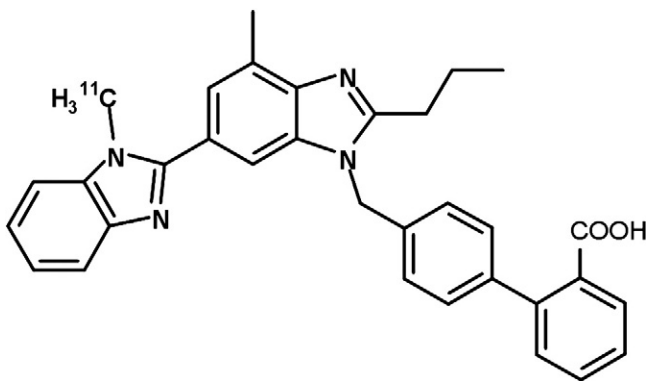

Fig. 1. Structure formula for [^{11}C]telmisartan.

Rats were anesthetized and maintained with a mixture of 1.5% isoflurane and nitrous oxide/oxygen (7:3). During anesthesia, body temperature were monitored and maintained at 37 °C. At the start of the emission scan, [^{11}C]telmisartan was administered as a single bolus via the tail vein in doses of 110±22 MBq/kg (n=3). The mass dose of [^{11}C]telmisartan for the bolus injection was calculated as 3.2±2.5 nmol/kg (n=3). An emission scan in 3D list-mode was performed for 90 min and the data were sorted into 75 dynamic sinograms according to the following sequence: 24 frame×5 s, 26 frame×30 s and 25 frame×180 s. All transaxial image slices were reconstructed using ordered subsets expectation maximization (OSEM) with 10 iterations and 19 subsets. ROIs representing liver and small intestines were delineated using the Pmod ver.3.0 program (PMOD Technologies Ltd, Zurich, Switzerland). Time–radioactivity curves (TACs) for each tissue were constructed by normalizing decay-corrected time–radioactivity measurements to the injected dose (% dose) of [^{11}C]telmisartan. TACs derived from PET scans in rats were converted to 73 kg human reference adult by correcting for the organ weight ratio using the following equation:

$$A_{human} = A_{rat} \times \frac{B_{rat}}{O_{rat}} \times \frac{O_{human}}{B_{human}} \quad (1)$$

in which A is the % injected activity within each organ, and O and B are weight of the organ and whole body, respectively. Extrapolating from the rat data using OLINDA/EXM [9] version 1.1 software by use of Medical Internal Radiation Dose (MIRD) methods [10], we estimated the effective dose of [^{11}C]telmisartan for humans(using tissue weighting factor based on ICRP 1990 [11]).

2.3. Human study

Six healthy volunteers (6 male; mean age±SD, 25±7 y; range, 20–38 y) participated in the study. Body weight of subjects was 58.5±2.8 kg (range, 54.9–63.2 kg) and body mass index was 20.2±2.0 kg/m^2 (range, 18.6–23.9 kg/m^2). All subjects were free of current medical and psychiatric illness based on history, physical examination, electrocardiogram, laboratory tests (including hematological examination, serum chemistry, urinalysis, and hepatitis B surface, hepatitis C virus and *Treponema pallidum* hemagglutination tests). We confirmed that they do not take drugs or dietary supplements, which may have an effect on pharmacokinetics, within 7 days. The study was approved by the ethics committee of Institute of Biomedical Research and Innovation. All subjects gave their written informed consent before participating in this study.

Serial PET scans were performed with ECAT EXACT HR + (Siemens/CTI, Knoxville, TN) dedicated PET scanner. The field of view (FOV) of the PET scanner covers 15.5 cm in axial direction and has a patient port of 56.2 cm. In the three-dimensional mode the average axial spatial resolution varies from 4.1 mm full-width at half-maximum (FWHM) in the center of FOV to 7.8 mm FWHM at 20 cm off-center [12].

The PET system was calibrated using a cylindrical phantom filled with ^{18}F-solution that had been measured in a calibrated dose calibrator to provide activity concentration in Bq/ml unit in the PET images [13].

Six subjects were scanned in the supine position with the arms beside the flanks. Before tracer injection, transmission data using three rotating solid ^{68}Ge-^{68}Ga rod sources were obtained on 8 bed positions (15.5 cm/bed position, 3.1 cm overlap, total axial length 1020 mm) from the head to the upper thigh to permit measured attenuation correction. The duration of each transmission scan was 3 min. At the start of PET scan, bolus of tracer solution and 20 ml of saline were infused during 60 s into the right median cubital vein. The mean administered [^{11}C]telmisartan mass dose was 1.05±0.25 micro g (range, 0.84–1.42 micro g n=6), and the mean injected activity was