JPP Journal of Pharmacy and Pharmacology

JPP 2010, 62: 456–461

Received August 18, 2009
Accepted October 24, 2009
DOI 10.1211/jpp/62.04.0007
ISSN 0022-3573

Research Paper

Therapeutic ^{188}Re-lanreotide: determination of radiopharmacokinetic parameters in rats

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Abstract

Objectives The radiopharmacokinetic parameters of the therapeutic radiopharmaceutical ^{188}Re-lanreotide were compared in rats implanted with hepatocarcinoma tumours ($n = 18$) and healthy rats ($n = 18$).

Methods Rats were injected with approximately 1.8 MBq ^{188}Re-lanreotide (0.1 ml) via the tail vein and blood samples were obtained. The activity per gram of tissue (%IA/g) was calculated and the radiopharmacokinetic parameters determined. Data were fitted using a two-compartment model.

Key findings Significant differences were found between healthy and hepatoma rats for beta elimination half-life (22.56 vs 48.14 h); transference constants K_{10} (k_e) (6.44 vs 3.05 h^{-1}) and K_{12} (2.76 vs 7.09 h^{-1}); volume of distribution (2.06 vs 5.45 ml); mean residence time (66.58 vs 95.50 h) and apparent volume of distribution at steady state (131.30 vs 810.37 ml). The tumour/organ ratios after 24 h were 11.20 for tumour/muscle, 8.00 for tumour/liver and 7.72 for tumour/bone. The scintigraphic images obtained therefore had high resolution.

Conclusions ^{188}Re-lanreotide had a prolonged beta elimination half-life and increased volume of distribution in rats with hepatocellular carcinoma. This may be beneficial in the diagnosis and therapy of metastatic lesions in patients with cancer.

Keywords ^{188}Re-lanreotide; radiopharmacokinetics; two-compartment pharmacokinetics

Introduction

Somatostatin is a natural human inhibitory hormone that regulates many functions, including blocking growth hormone, thyroid-stimulating hormone, insulin and glucagon. Most human tumours over-express one of the five known distinct subtypes of somatostatin receptor; hepatomas over-express all five receptors that bind the somatostatin hormone.

Somatostatin has been used for the treatment of neuroendocrine tumours but it is not suitable for clinical use because it is denatured in the body within seconds. Hence, long-lived analogues have been synthesised such as octreotide, which binds to the same somatostatin receptors with higher affinity, similar activity and longer therapeutic effects.

As a chemotherapeutic agent for peptide-receptor-mediated therapy, octreotide has been used successfully in the treatment of malignant carcinoid and other endocrine tumours.[1,2] The octreotide molecule with a tyrosine residue (TOC) has been radiolabeled with iodine (^{131}I-TOC) for localising solitary tumour metastases by in-vivo somatostatin receptor scintigraphy. The octapeptide lanreotide is used in the management of symptoms caused by acromegaly, neuroendocrine tumours, malignant carcinoid tumours and VIPomas that arise in or near the adrenal gland and over-express somatostatin receptors. Lanreotide also shows activity against non-endocrine tumours and is being studied as a possible general antitumour agent.[3–5]

Octreotide, lanreotide and other small somatostatin analogues that bind specifically, effectively and persistently to the target tumour cell receptors and internalise in the cytoplasm

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and cell nuclei can be easily labelled with gamma emitters such as technetium-99m, indium-111, gallium-68 and rhenium-188 (^{188}Re) and are suitable for imaging malignant tumour lesions and metastatic foci that may not be seen by conventional imaging techniques. The same peptides labelled with beta-emitter radionuclides (yttrium-90, rhenium-188, lutetium-177, indium-113) are used for neuroendocrine tumour therapy.[3,4,6–11] ^{188}Re is a radionuclide that allows both imaging and therapy; it is a gamma (155 keV) and beta (2.19 keV) emitter with a 16.98 h disintegration half-life. It is easily obtained in a hospital radiopharmacy from a tungsten–rhenium generator (^{188}W–^{188}Re).[12,13] Lanreotide has been directly labelled with ^{188}Re[14–18] and successfully used for therapy.[3,4,8,19,20] The peptide in micro- or nanomolar amounts carries radionuclide to the target cell receptors but does not have a pharmacological effect *per se,* and a special branch of pharmacokinetics is used to study its biodistribution. The radiopharmacokinetic parameters are determined by detecting the radiation emitted from the labelled peptide. The experimentally obtained parameters are fitted to a hypothetical model for a specific pathology; however, this model is not reliable if it is not verified by mathematical methods.

Liver cancer is not easily diagnosed or treated and is generally fatal; thus an Re radiopharmaceutical might be useful for scintigraphy, dosimetry and therapy.[8,10,20] In this study we determined the radiopharmaceutical parameters of ^{188}Re-lanreotide following a single intravenous dose to Wistar rats with hepatocellular carcinoma (HCC). The experimentally obtained biodistribution and organ uptake in healthy rats and rats with HCC was used as the input for the WinNonlin program (2000, Pharsight Corp., CA, USA).

The rat model is useful to determine the pharmacokinetic parameters and the tumour/organ ratios of ^{188}Re-lanreotide to be used for calculating the individual dose following the medical internal radiation dose (MIRDOSE) methodology and later in the diagnosis and therapy of metastatic lesions in patients with cancer.

Material and Methods

Preparation of ^{188}Re-lanreotide

Lanreotide [3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threonine-amide] and cyclic(2→7)-disulfide(9Cl) from Sigma-Aldrich Corp. (St Louis, MO, USA) was labelled with ^{188}Re by a modified direct method using (1-1-diphosphoric acid (HEDP) as a weak competing ligand and stannous chloride ($SnCl_2$) to reduce both Re and the peptide's disulfide bridge for metal chelating.[15,17,18] Lanreotide (0.027 mg) in 0.1 ml sterile apyrogenic water, 1.7 mg HEDP in 0.1 ml of the same water for injection and 0.21 mg of $SnCl_2 \cdot 2H_2O$ in 0.1 ml 12 N HCl were mixed in a glass vial. The mixture was labelled with approximately 166.3 MBq (4.5 mCi) in 0.78–1.0 ml $^{188}ReO_4^-$ eluted from an ^{188}W–^{188}Re generator (Oak Ridge National Laboratories, TN, USA). The reaction was carried out at pH 2 with 90 min incubation period in boiling water. Before injection, the pH was raised to pH 7.2 using citrate buffer. The radioactivity was measured using a CRC-15R dose calibrator (Capintec, NJ, USA).[17]

Radiochemical purity

Radiochemical impurities in the ^{188}Re-lanreotide were identified by chromatography using ITLC silica-gel (SG)-impregnated glass-fibre strips (Gelman Sciences, Inc./Pall Corp., Ann Arbor, MI, USA) with three solvents: 0.9% NaCl, acetone, and acid ethanol (10% 0.3 mol/l HCl). The radiochemical stability was evaluated immediately and 24 h after preparation by the same method.

Animal model

Biodistribution and radiopharmacokinetic studies in Wistar rats were carried out according to the rules and regulations of the official Mexican standard 062-ZOO-1999.[21] Male Wistar rats (200–300 g) maintained on standard PMI 5001 feed (Purina) were used according to the rules and regulations of the Institute for Radiopharmacokinetic Studies. They were kept in plastic cages with wood-shaving bedding. Temperature was maintained at 21°C and humidity at 50–60%, with a 12 h light–dark cycle and subdued noise. Water and feed were provided *ad libitum.*

Propagation of hepatoma AS-30D cells and tumour induction in rats

AS-30D hepatoma cells were obtained from the ascites of a Wistar rat with HCC and were propagated in the peritoneal cavity of normal rats.[22] Rats developed ascites after 7 days. The process for propagation of AS-30D murine hepatoma cells was repeated two or three times.[23–28] A sample of ascites was cultured for bacterial contamination and histopathological slides were used to confirm the liver cancer cell line.

AS-30D cells were obtained by centrifugation of 5 ml pooled ascites. Then, 1 million cells in 0.1 ml phosphate buffered saline were injected subcutaneously into the dorsal side of healthy rats. The injection sites were monitored for both the propagation cells in the peritoneum and the implanted hepatoma tumour. Studies were carried out 60 days after inoculation, when the tumours were 0.5–1 cm in diameter and 1.5 g.[22] Pathology studies confirmed that tumours induced with AS-30D cells were due to a carcinogenic process and not to a foreign body reaction.

Biodistribution studies

Healthy rats and HCC-bearing rats were used for distribution and radiopharmacokinetic studies. ^{188}Re-lanreotide, approximately 1.8 MBq (48.6 μCi) in 0.1 ml, was injected into the peritoneal cavity and in the left dorsal side of healthy rats. The rats (n = 3 per time point) were killed at 0.083, 0.25, 0.5, 1.16, 3 and 24 h after the injection. The heart, spleen and kidneys and samples of lung, liver, stomach, intestines, muscle, bone and tumour were rinsed with saline, blotted on paper and placed into pre-weighed plastic test tubes. The radioactivity in the organs and aliquots of blood and ascites was determined in a well-type scintillation detector (Canberra, Meriden, CT, USA) along with six 0.25 ml samples of the diluted standard representing 100% of the injected activity. The mean activity was used to obtain the percentage of injected activity per g tissue (%IA/g).

Radiopharmacokinetic parameters

The activity of all the blood samples taken at 0.25, 0.5, 1.1, 3, 5, 8, 12, 15, 18 and 24 h for healthy rats and 0.25, 0.5, 1.16, 3 and 24 h for tumour-bearing rats were used as the input data for the WinNonlin program to calculate the radiopharmacokinetic parameters for a two-compartment model following a single intravenous bolus dose. The following parameters were determined: α and β elimination constants, area under the curve (AUC), α and β half-lives, transference constants (k_{12}, k_{21}, k_{10}), apparent volume of distribution (V_d), total clearance (Cl), mean residence time (MRT) and apparent volume of distribution at steady state (V_{ss}).

Histopathological studies

Histopathological studies were carried out to determine the histological nature of the tumour (cancer, inflammation, infection). Fragments (2.0 g) of the tumours (n = 5) were fixed in formol, embedded in paraffin, cut into thin slices (0.05 μm) and stained with haematoxylin and eosin.

Statistical analysis

Net counts per minute (radioactive counts per min) and g of tissue data obtained were used to calculate IA/g tissue for each organ and for each time interval from each rat. The mean net counts per min of the diluted standard representing 100% of the injected activity was used to calculate %IA/g tissue.

Ratios of the %IA/g found for tumour/blood, tumour/muscle, tumour/bone, tumour/ascites and tumour/liver for the 3 h and 24 h time periods were calculated (n = 3 rats).

Differences were determined using the Student's t-test and F distribution, with significance set at $P < 0.05$. The Kruskal–Wallis test was used to compare the distribution of ^{188}Re-lanreotide in healthy rats and tumour-bearing rats and to see that the samples of cells in healthy rats come from different populations compared with tumour-bearing rats.

Results

Preparation and radiochemical purity of ^{188}Re-lanreotide

The radiopharmaceutical was prepared with approximately 166.3 MBq $^{188}ReO_4^-$. The radiochemical purity determined by the ITLC-SG system with the three solvents was 96 ± 3% up to 24 h. The radiochemical impurities were 2 ± 1% for ^{188}Re-HEDP, and <1% for ^{188}Re-O_2 and ^{188}Re-O_4^-.

Biodistribution

Blood clearance in healthy rats was rapid, with rapid elimination. The kidney/blood ratio was 45.86 after 3 h and 1.83 after 24 h, showing, that as with many labelled peptides, the dose-limiting organ is the kidney. Biodistribution and uptake in all organs and biological fluids in healthy rats and tumour-bearing rats are summarized in Tables 1 and 2.

The mean concentration ratios of the tumour/organs of interest 24 h after injection were: 3.73 for tumour/blood; 11.20 for tumour/muscle; 7.72 for tumour/bone; 3.73 for tumour/ascites and 8.00 for tumour/liver (Figure 1). The radiopharmacokinetic profile of ^{188}Re-lanreotide in healthy and tumour-bearing rats is shown in Figure 2.

Radiopharmacokinetic parameters

A two-compartment first-order elimination model was used to estimate the pharmacokinetic parameters of ^{188}Re-lanreotide in healthy and tumour-bearing rats using the WinNonlin program: initial activity (i.e. %IA/g tissue), β elimination half-life, K_{10} (ke) and K_{12} transference constants, V_d, MRT and V_{ss} were significantly different between the two groups (Table 3; t = 5.65E − 0.06, F = 0.028; $P < 0.05$).

Histopathological studies

The histopathological studies confirmed the diagnosis of epithelial tumour compatible with rat-induced hepatoma. The microscopic slides of ascites show abundant nests of atypical epithelial neoplastic cells with round pleomorphic hyperchromatic nuclei and variable amounts of cytoplasm. No mitosis, nor red blood cells or bacteria were seen in the smears. The cells in the peritoneum were from tumours. AS (30D) tumour cells, as well as hepatocarcinoma cells, possess fewer mitochondria than healthy cells.

Statistical strategy

The Kruskal–Wallis test indicated that the probability of having a value of $H \geq 70.89$ is less than 0.004, so there is a

Table 1 Biodistribution of ^{188}Re-lanreotide in healthy rats

	Time (h)					
	0.083	0.25	0.5	1.166	3	24
Blood	–	4.9070 ± 0.0090	0.5510 ± 0.0015	0.0745 ± 0.0007	0.0568 ± 0.0026	0.0295 ± 0.0007
Heart	0.0450 ± 0.0070	0.0790 ± 0.0007	0.0240 ± 0.0021	0.0083 ± 0.0011	0.0016 ± 0.0006	0.0595 ± 0.0007
Lung	0.1500 ± 0.0700	0.6290 ± 0.0063	0.1040 ± 0.0056	0.0405 ± 0.0064	0.3100 ± 0.0141	0.1600 ± 0.0141
Liver	0.1850 ± 0.0070	1.1610 ± 0.0714	0.1840 ± 0.0198	0.0600 ± 0.0070	0.9300 ± 0.0283	0.2700 ± 0.0141
Spleen	0.0350 ± 0.0070	0.0500 ± 0.0070	0.0250 ± 0.0007	0.0120 ± 0.0014	0.0595 ± 0.000	0.2850 ± 0.0070
Stomach	0.0250 ± 0.0070	0.4530 ± 0.0460	0.0220 ± 0.0028	0.0385 ± 0.0021	1.400 ± 0.2828	0.1200 ± 0.0141
Small intestine	0.0550 ± 0.0070	0.9090 ± 0.0042	0.0380 ± 0.0035	1.0350 ± 0.0212	0.0095 ± 0.0007	0.1400 ± 0.0141
Large intestine	0.0350 ± 0.0070	0.8210 ± 0.0318	0.0910 ± 0.0014	0.9880 ± 0.0113	0.0105 ± 0.0007	0.0885 ± 0.0021
Kidney	0.1850 ± 0.0070	0.6550 ± 0.0332	0.1780 ± 0.0028	0.1655 ± 0.0077	2.1200 ± 0.1697	5.3900 ± 0.5515
Muscle	0.0155 ± 0.0060	0.0530 ± 0.0028	0.0105 ± 0.0007	0.0079 ± 0.0001	0	0.0160 ± 0.0028
Bone	0.1350 ± 0.0070	0.0634 ± 0.0018	0.1040 ± 0.0070	0.0295 ± 0.0007	0.0215 ± 0.0007	0.9750 ± 0.0070

Values are activity per gram of tissue (%IA/g), means ± SD (n = 3).

Table 2 Biodistribution of ^{188}Re-lanreotide in rats with liver cancer

	Time (h)					
	0.083	0.25	0.5	1.166	3	24
Blood	–	1.4960 ± 0.0100	0.1730 ± 0.0100	0.0430 ± 0.0120	0.0580 ± 0.0100	0.0600 ± 0.0100
Heart	0.0360 ± 0.0160	0.0415 ± 0.0007	0.0240 ± 0.0100	0.0080 ± 0.0020	0.1100 ± 0.0700	0.0820 ± 0.0100
Lung	0.0415 ± 0.0100	0.3355 ± 0.0290	0.0600 ± 0.0200	0.0450 ± 0.0100	0.3200 ± 0.0100	0.0130 ± 0.0100
Liver	0.1000 ± 0.0100	3.3300 ± 0.1400	0.2500 ± 0.1100	0.0600 ± 0.009	0.9500 ± 0.0100	0.0280 ± 0.0100
Spleen	0.0500 ± 0.0200	0.0240 ± 0.0100	0.0400 ± 0.0200	0.0130 ± 0.0007	0.0400 ± 0.0200	0.0290 ± 0.0100
Stomach	0.0090 ± 0.0100	0.0070 ± 0.0010	0.0450 ± 0.0030	0.0450 ± 0.0040	0.1100 ± 0.0120	0.0090 ± 0.0001
Small intestine	0.0590 ± 0.0060	0.1960 ± 0.0190	0.0600 ± 0.0050	1.5300 ± 0.4300	0.1560 ± 0.0100	0.5900 ± 0.0890
Large intestine	0.0430 ± 0.0100	0.2670 ± 0.0110	0.0580 ± 0.0200	0.0150 ± 0.0120	0.0350 ± 0.0110	0.0030 ± 0.1000
Kidney	0.1430 ± 0.0137	0.2100 ± 0.0200	0.2200 ± 0.0110	0.1700 ± 0.0400	2.6600 ± 0.1230	0.1100 ± 0.0090
Muscle	0.0190 ± 0.0090	0.0550 ± 0.0040	0.0060 ± 0.0001	0.0050 ± 0.0002	0.0270 ± 0.0010	0.0200 ± 0.0010
Bone	0.0110 ± 0.0010	0.0060 ± 0.0010	0.0100 ± 0.0011	0.0290 ± 0.0050	0.2200 ± 0.0110	0.0290 ± 0.0100
Tumour	0.0240 ± 0.0014	0.3050 ± 0.0120	0.0150 ± 0.0007	0.0350 ± 0.0020	0.0600 ± 0.0020	0.2240 ± 0.1500
Ascites	0.0060 ± 0.0020	0.0730 ± 0.0100	0.0550 ± 0.0007	0.0120 ± 0.0040	0.0700 ± 0.0029	0.0600 ± 0.0140

Values are activity per gram of tissue (%IA/g), means ± SD (n = 3).

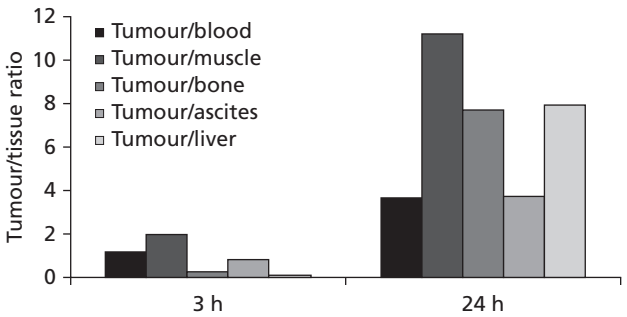

Figure 1 Tumour/tissue concentration ratios of ^{188}Re-lanreotide in rats with induced hepatoma. Ratios at 24 h were: tumour/blood 3.73, tumour/muscle 11.20, tumour/bone 7.72, tumour/ascites 3.73, tumour/liver 8.00

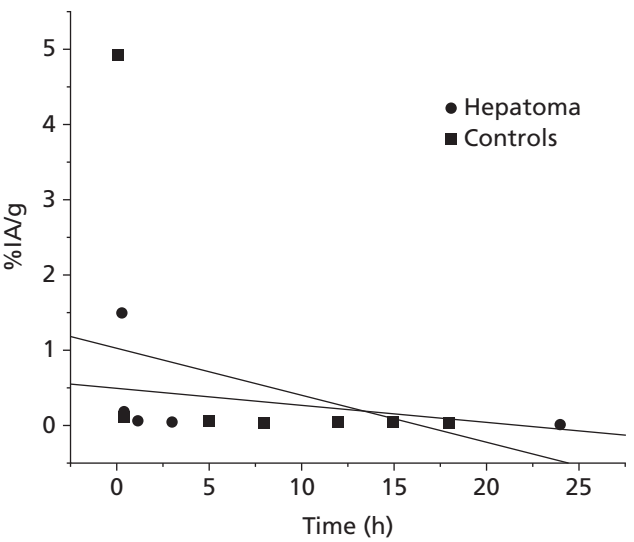

Figure 2 Radiopharmacokinetic profile in rats with hepatoma and healthy rats. Blood concentration–time curve following i.v. bolus administration of ^{188}Re-lanreotide (approx. 1.8 MBq/g, considering dose as 100% activity). Profiles were obtained from experimental data for blood using the WinNonlin program

difference in the biodistribution in healthy rats compared with tumour-bearing rats.

Discussion

The murine hepatoma AS-30D cell line, which over-expresses somatostatin receptors,[22–28] was used to grow a tumour and produce ascites in Wistar rats in order to study the biodistribution, pharmacokinetic parameters and profile of ^{188}Re-lanreotide. The β elimination half-life, transference constants, V_d, MRT and V_{ss} were significantly different between the control rats and tumour-bearing rats (Table 3). These differences may be due to ^{188}Re-lanreotide in the ascites in rats with the implanted HCC.

Histopathology studies showed that cancer cells had some deformation of the cell membrane and hyperchromatic nuclei.

The Kruskal–Wallis test was used to confirm that ^{188}Re-lanreotide was distributed in different organs and that the samples were from different populations (assuming the null hypothesis that the samples are from identical populations; the alternative hypothesis assumes that the sample came from different populations in healthy and tumour-bearing rats).

The radiopharmacokinetic parameters conformed to the traditional two-compartment model: a central compartment (blood) and a peripheral compartment comprising less-perfused organs, with first-order elimination from the central compartment. The Akaike criterion and the correlation coefficient calculated by the WinNonlin program determined the goodness of fit. This model provided a conceptual framework of drug disposition that better matches the behaviour of ^{188}Re-lanreotide in healthy and tumour-bearing rats. ^{188}Re-lanreotide has been reported to have favourable biodistribution and specific binding to some tumours[18] but showed low affinity for the liver tumour (Table 2). However, the tumour/organ ratios were high (Figure 1). The 11-fold activity for the tumour over the muscle or background activity means that the tumour could be visualised with high resolution using a gamma camera. Also, the HCC could be

Table 3 Radiopharmacokinetic parameters of ^{188}Re-lanreotide in rats

	Healthy rats			Rats with hepatoma		
	Estimated	SE	%CV	Estimated	SE	%CV
A (%μCi/g ml)	48.58	1.05	2.17	18.30	0.03	0.14
B (%μCi/g ml)	0.07	0.01	10.50	0.06	0.00	0.18
α elimination constant (h^{-1})	9.23	0.09	0.97	10.18	0.01	0.06
β elimination constant (h^{-1})	0.04	0.01	37.39	0.02	0.00	1.04
AUC (%μCi/g ml*h)	7.54	0.24	3.20	6.01	0.07	1.12
K_{10}-HL (h)	0.11	0.00	3.50	0.23	0.00	1.19
α-HL (h)	0.08	0.00	0.44	0.07	0.00	0.09
β-HL (h)	22.55	3.10	13.76	48.14	0.85	1.77
K_{10} (1/h)	6.44	0.23	3.49	3.05	0.04	1.20
K_{12} (1/h)	2.76	0.21	7.61	7.09	0.03	0.48
K_{21} (1/h)	0.04	0.01	10.58	0.05	0.00	0.64
Vd (ml)	2.06	0.02	0.99	5.45	0.01	0.23
C_p^0 (%μCi/g ml)	48.61	0.48	0.99	18.34	0.04	0.23
Cl (ml/h)	13.26	0.42	3.20	16.63	0.19	1.13
AUMC (%μCi/g ml*h)^2	74.73	18.07	24.17	293.06	9.89	3.37
MRT (h)	66.58	2.09	3.134	95.50	1.10	1.15
V_{ss} (ml)	131.30	23.63	18.00	810.37	9.39	1.16

Values were determined using a two-compartment model and the experimentally obtained blood data ($n = 3$) using the WinNonlin program. A, initial %IA/g tissue, determined by extrapolation to the intercept on the ordinate axes A; B, %IA/g tissue determined by extrapolating to the intercept the ordinate axes B; K10-HL, α-HL, β-HL, times of k10, α and β microconstants; AUC, area under the curve; k_{12}, k_{21}, k_{10}, transference constants; Cl, clearance; C_p^0, initial %IA/g; Cl, total clearance; AUMC, area under the curve in the second moment; MRT, mean residence time; Vd, apparent volume of distribution; V_{ss}, apparent volume at steady state.

easily detected, having eightfold higher activity than the liver tissue. Images of bone metastasis were also conclusive.

Lanreotide and other somatostatin peptide analogues are used in gram concentrations for therapeutic purposes. The radiopharmaceutical is prepared with 27 μg of the lanreotide peptide. The radionuclide carried by micro- or nanomolar amounts of peptide to the target cell receptors does not have a pharmacologic effect *per se* but, because of the Re^{188} beta radiation, there is damage in the cytoplasm or nuclei of the receptor-bearing cells, which mainly affects apoptosis.[29] In comparison with the widely used yttrium-90 (pure beta emitter), ^{188}Re offers the advantages of a short half-life, a lower absorbed radiation dose and, because it is also a gamma emitter, it can image tumours and metastases. For therapeutic purposes, ^{188}Re-lanreotide would be useful because it is specifically concentrated in liver tumours and it may prevent ascites formation. The determination of ^{188}Re-lanreotide radiopharmacokinetic parameters, mainly the MRT and the effective half-life, is necessary to estimate the activity for individual radiopharmaceutic therapy following the MIRDOSE methodology.

Conclusions

The two-compartment model is the simplest tool available for elaborating a pharmacokinetic profile of ^{188}Re-lanreotide in healthy and tumour-bearing rats. The experimental radiochemical and radiopharmacobiological characteristics of ^{188}Re-lanreotide, as shown in the animal model, and specifically the MRT (calculated from the injected activity and uptake by the organ of interest) and mean half-life could be used to calculate the therapeutic dose following MIRDOSE methodology to be administered in patients with cancer.

The biodistribution of ^{188}R-lanreotide was different in tumour-bearing rats compared with healthy rats. The high tumour/muscle, tumour/liver and tumour/bone ratios observed indicate that scintigraphy images of soft tissue, liver or bone tumours and metastases can be obtained and can be seen with clarity and high resolution.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Acknowledgements

We thank the International Atomic Energy Agency (IAEA); the Consejo Nacional de Ciencia y Tecnología (CONACyT-México), SEP-CONACyT 61-541 and Dr Edilso Reguera Ruíz for the realisation of this study.

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