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Original Article

Preliminary absorbed dose evaluation of two novel ^{153}Sm bone-seeking agents for radiotherapy of bone metastases: comparison with ^{153}Sm-EDTMP

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Abstract

Aim: The amount of energy deposited on any organ by ionising radiation termed *absorbed dose*, plays an important role in evaluating the risks associated with the administration of radiopharmaceuticals. In this research work, the absorbed dose received by human organs for ^{153}Sm-TTHMP and ^{153}Sm-PDTMP was evaluated based on biodistribution studies on the Syrian rats.

Materials and methods: ^{153}Sm-TTHMP and ^{153}Sm-PDTMP were successfully prepared with radiochemical purity of higher than 99%. The biodistribution of the complexes was investigated within the Syrian rats up to 48 hours post injection. The human absorbed dose of the complexes was estimated by the radiation dose assessment resource method.

Results: The highest absorbed dose for ^{153}Sm-TTHMP and ^{153}Sm-PDTMP was observed in the trabecular bone with 1·085 and 1·826 mGy/MBq, respectively. The bone to other critical organ dose ratio for ^{153}Sm-PDTMP is significantly greater than ^{153}Sm-TTHMP. Also, the bone/red marrow dose ratio for these complexes is comparable with this ratio for ^{153}Sm-EDTMP, as the most clinically used Sm-153 bone pain palliative radiopharmaceutical.

Findings: According to the considerable bone absorbed dose against the insignificant absorbed dose of non-target organs, these complexes can be used as potential bone pain palliative agents in clinical applications.

Keywords: internal dosimetry; PDTMP; RADAR method; Sm-153; TTHMP

INTRODUCTION

Metastatic bone cancer is a common and severe complication in advanced diseases.[1,2] It develops in up to 70% of patients with prostate cancer and breast cancer, and in up to 30% of those with cancers of the lung, bladder and thyroid.[3,4] In these patients who have progressive disease despite treatment, a systemic bone-avid radiopharmaceutical for treatment of widespread bony metastases has obvious potential benefits.[5]

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Nowadays, many radiopharmaceuticals are developed for treatment of painful metastases. An impressive array of radionuclides such as ^{32}P, ^{89}Sr, ^{186}Re, ^{188}Re, ^{153}Sm, ^{166}Ho and ^{177}Lu is used to develop these radiopharmaceuticals. β^- particles of low energies are recommended for bone pain palliation, whereas those with higher energies are used for the bone marrow ablation.[6] The most important point that should be considered in developing radiopharmaceuticals as the bone pain palliative or the bone marrow ablative agents is the dose delivered to the bone marrow.

Among the therapeutic radionuclides, ^{153}Sm with the favourable radiation characteristics [$t_{1/2} = 1{\cdot}93d$, $\beta_{max} = 0{\cdot}81$ MeV (20%), 0·71 MeV (49%), 0·64 MeV (30%) and $\gamma = 103$ keV (30%)],[7] is the most widely used radionuclide for radiotherapy of the bone metastases in the form of ^{153}Sm-EDTMP (Lexidronam) in the United States.[8] However, other ^{153}Sm bone-seeking agents have been developed paving the way for better pharmacokinetics with less side effects. ^{153}Sm-triethylene tetramine hexa (methylene phosphonic acid) (^{153}Sm-TTHMP) and ^{153}Sm-propylene di-amino tetra methy1ene-phosphonicacid (^{153}Sm-PDTMP) are the novel reported agents indicated as potential for clinical applications.[9,10]

The main goal in radiotherapy is to deliver the absorbed dose to the target organs in the highest possible amount, while as regards the other organs, especially within the critical organs, the absorbed dose is kept as low as possible. The absorbed dose plays an important role in evaluating the risks associated with the administration of radiopharmaceuticals and thus the maximum amount of activity that should be undertaken.[11] Nowadays, in nuclear medicine, the most commonly used procedure for making the internal dose estimates is the radiation dose assessment resource (RADAR) method.[12]

In this piece of research work, for better evaluation of the therapeutic effects of ^{153}Sm-TTHMP and ^{153}Sm-PDTMP, these complexes were prepared and their biodistribution in the Syrian rats were studied up to 48 hours post injection. In addition, with regard to the importance of the absorbed dose in developing new therapeutic agents, the absorbed dose to human organs for these complexes was evaluated based on biodistribution studies on rats by RADAR method and was compared with ^{153}Sm-EDTMP as the most clinically used bone pain palliative agent.

MATERIALS AND METHODS

Samarium-152 with purity of >98% was obtained from ISOTEC Inc. (Miamisburg, Ohio, USA). ^{153}Sm was produced by ^{152}Sm (n, γ) ^{153}Sm nuclear reaction. All chemicals were purchased from Sigma-Aldrich Chemical Co. Whatman No. 2 paper was obtained from Whatman (UK). Radiochromatography was performed by using a thin layer chromatography scanner, Bioscan AR2000 (Paris, France). A high purity germanium (HPGe) detector coupled with a Canberra™ (model GC1020-7500SL, Oak Ridge, USA) multichannel analyzer and a dose calibrator ISOMED 1010 (Dresden, Germany) were employed for counting distributed activity in the rat organs. Calculations were based on the 103 keV peak for ^{153}Sm. All values were expressed as mean ± standard deviation (mean ± SD) and the data were compared using Student's *t*-test. Statistical significance was defined as $p < 0{\cdot}05$. Animal studies were performed in accordance with the UK Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd edition.

Production and quality control of $^{153}SmCl_3$

One milligram of enriched $^{152}Sm_2O_3$ (^{152}Sm, 98·7% from ISOTEC Inc.) was irradiated in a thermal neutron flux of 5×10^{13} n/cm^2/second in a research reactor. The irradiated target was dissolved in 100 µL of 1·0 M HCl, to prepare $^{153}SmCl_3$. The solution was filtered through a 0·22 µm filter (Millipore, Millex GV, County Cork, Irland). The radionuclidic purity of the solution was checked utilising β spectroscopy as well as HPGe spectroscopy. Also the radiochemical purity of the $^{152}SmCl_3$ was studied using instant thin layer chromatography (ITLC) method by two solvent systems [A: 10 mM DTPA pH 4 and B: ammonium acetate 10%: methanol (1:1)].

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Preparation and quality control of ^{153}Sm-TTHMP and ^{153}Sm-PDTMP

^{153}Sm-TTHMP and ^{153}Sm-PDTMP were prepared according to the previously mentioned procedure.[10] Briefly, a stock solution was prepared by dissolving specified values of TTHMP and PDTMP (250, 200, 150, 100, 50, 10 mg) in 1·5 mL NaOH (2 N) and 3·5 mL distilled H_2O. Then 300 μL of the stock solution was added to 200 μL of $^{153}SmCl_3$ (210 MBq). The effect of pH was investigated by adjustment with phosphate buffer. The reaction mixtures were incubated by stirring at room temperature for 2 hours. The radiolabeling yield of the ligand was determined with paper chromatography employing Whatman No. 2 paper in NH_4OH:MeOH:H_2O (2:20:40) mixture.

Biodistribution of ^{153}Sm-TTHMP and ^{153}Sm-PDTMP in wild-type rats

Two-hundred microlitre of final ^{153}Sm-TTHMP and ^{153}Sm-PDTMP solutions with 5·55 MBq radioactivity were injected intravenously into rats through their tail vein. The total amount of the injected radioactivity into each animal was measured by counting the syringe before and after injection in a dose calibrator with fixed geometry. The animals were sacrificed at the exact time intervals (2, 4, 24, 48 hours). The activity concentration (A) of each tissue was calculated using an HPGe detector as[13]

$$A = \frac{N}{\epsilon\gamma t_s m k_1 k_2 k_3 k_4 k_5} \quad (1)$$

where, ε is the efficiency at photopeak energy, γ is the emission probability of the γ line corresponding to the peak energy, t_s is the live time of the sample spectrum collection in seconds, m is the mass (kg) of the measured sample, k_1, k_2, k_3, k_4 and k_5 are the correction factors for the nuclide decay from the time the sample is collected to start the measurement, the nuclide decay during counting period, self-attenuation in the measured sample, pulses loss due to random summing and the coincidence, respectively. N is the corrected net peak area of the corresponding photopeak given as

$$N = N_s \frac{t_s}{t_b} N_b \quad (2)$$

where N_s is the net peak area in the sample spectrum, N_b is the corresponding net peak area in the background spectrum and t_b is the live time of the background spectrum collection in seconds.

The percentage of the injected dose per gram (%ID/g) for different organs was calculated by dividing the activity concentration of each tissue (A) to the injected activity and the mass of each organ. Five rats were sacrificed for each time interval. All values were expressed as mean ± standard deviation and the data were compared using Student's t-test.

Calculation of accumulated activity in human organs

The accumulated source activity for each organ of animals was calculated according to Equation (3), where A (t) is the activity of each organ at time t:

$$\tilde{A} = \int_{t_1}^{\infty} A(t)dt \quad (3)$$

For this purpose, the data points representing the percentage-injected dose were created. A linear approximation was made between the two experimental points of times. The curves were extrapolated to infinity by fitting the tail of each curve to a monoexponential curve with the exponential coefficient equal to physical decay constant of ^{153}Sm. The accumulated activity was calculated by computing the area under the curves.

The accumulated activity in the animals was extrapolated to the accumulated activity in humans by the proposed method of Sparks et al. [Equation (3)]:[14]

$$\tilde{A}_{\text{human organ}} = \tilde{A}_{\text{animal organ}} \times \frac{\frac{Organmass_{human}}{Bodymass_{human}}}{\frac{Organmass_{animal}}{Bodymass_{animal}}} \quad (4)$$

In order to extrapolate this accumulated activity to human, the standard mean weights of each organ for human and rat were used (Table 1).[12,15]

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Table 1. The mean weights of organs for human and rat

Organ	Human organ weight (g)	Rat organ weight (g)
Bone	6120	1·90
Heart	316	0·65
Stomach	158	0·99
Kidneys	229	1·47
Small intestine	1,100	3·80
Spleen	183	0·68
Muscle	28,000	101·53
Liver	1,910	8·13
Lungs	1,000	1·24
Total body	73,700	190

Absorbed dose calculation

The absorbed dose in human organs was calculated by RADAR formalism based on biodistribution data in the rats:[12]

$$D = \tilde{A} \times DF \quad (5)$$

where $\tilde{A}$ is the accumulated activity for each human organ, and DF is

$$DF = \frac{k \sum_i n_i E_i \phi_i}{m} \quad (6)$$

where n_i is the number of radiations with energy E emitted per nuclear transition, E_i is the energy per radiation (MeV), ϕ_i is the fraction of energy emitted that is absorbed in the target, m is the mass of the target region (kg) and k is some proportionality constant $\left(\frac{mGy \cdot kg}{MBq \cdot s \cdot MeV}\right)$. DF represents the physical decay characteristics of the radionuclide, the range of the emitted radiations, and the organ size and configuration[16] expressed in mGy/MBq·s. DFs have been taken from the OLINDA/EXM software.[12] It should be notified that D in Equation (5) is the absorbed dose in the target organ from a source organ and as a result, the total absorbed dose for each target organ was computed by the summation of the absorbed dose received from each source organ.

RESULTS AND DISCUSSION

Production and quality control of $^{153}SmCl_3$

The radionuclide was prepared in a research reactor with a specific activity of 12·8 GBq/mg. After counting the samples on an HPGe detector, radionuclidic purity was higher than 99·99% [$^{154}Eu < 4{\cdot}7 \times 10^{-5}$% of ^{153}Sm and $^{155}Eu < 2{\cdot}4 \times 10^{-5}$% of ^{153}Sm]. Radiochemical impurities in the ^{153}Sm sample used in the radiolabeling step were checked by the two solvent systems. Whatman No. 2 was used as a stationary phase for paper chromatography system. In %10 ammonium acetate:methanol, the free samarium cation in $^{153}Sm^{3+}$ form remained at the origin ($R_f = 0{\cdot}0$), while other ^{153}Sm species migrated to higher R_fs (0·8). Another eluent for $^{153}Sm^{3+}$ detection was 10 mM DTPA aqueous solution at pH 3 ($R_f = 0{\cdot}8$).

Table 2. The optimised conditions for radiolabeling of ^{153}Sm-TTHMP and ^{153}Sm-PDTMP

Bone-seeking agent	Ligand/metal ratio concentration	pH	Time (minutes)	Temperature (°C)
^{153}Sm-PDTMP	274:1	7–8	60	22
^{153}Sm-TTHMP	365:1	7–8	60	22

Quality control of ^{153}Sm-TTHMP and ^{153}Sm-PDTMP

In order to obtain maximum complexation yield, several experiments were carried out by varying different reaction parameters such as ligand concentration, pH and reaction time. The optimised condition for radiolabeling of ^{153}Sm-PDTMP and ^{153}Sm-TTHMP are given in Table 2. The radiolabeled complexes were prepared by radiochemical purity of higher than 99% in the optimised conditions. ITLC chromatograms of $^{153}SmCl_3$ and radiolabeled solutions in NH_4OH: MeOH: H_2O (2:20:40) are shown in Figure 1.

Biodistribution of radiolabelled compounds in Syrian rats

The animals were sacrificed by CO_2 asphyxiation at the selected times after injection (2, 4, 24 and 48 hours). Dissection began by drawing blood from the aorta followed by removing the heart, spleen, muscle, bone, kidney, liver, intestine, stomach, lung and skin samples. The tissue uptakes were calculated as the percentage of the area under the curve of the related photopeak per gram of the tissue (%ID/g; Tables 3 and 4). The non-decay-corrected clearance curves from the

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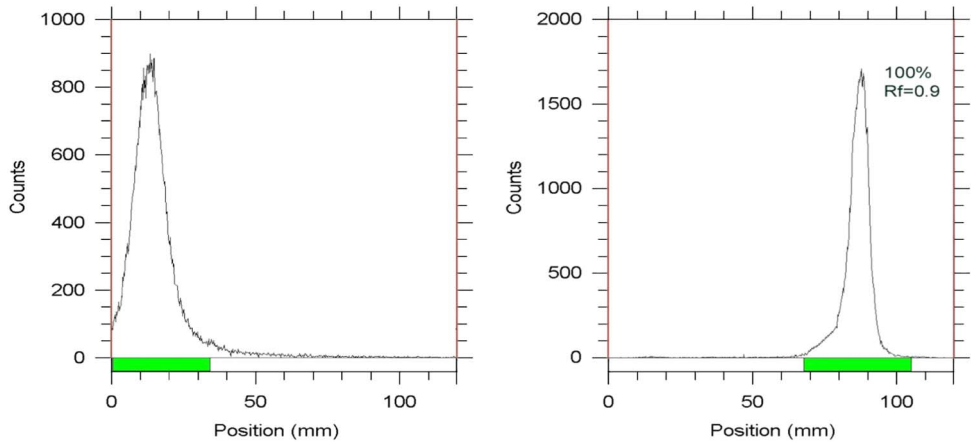

Figure 1. ITLC chromatograms of $^{153}SmCl_3$ (left) and radiolabeled compounds (right) on Whatman No. 2 paper using NH_4OH: $MeOH$:H_2O (0·2:2:4). Abbreviations: ITLC, instant thin layer chromatography.

Table 3. *Percentage of injected dose per gram (ID/g %) after intravenous administration of 5·55 MBq ^{153}Sm-PDTMP in Syrian rat tissues at 2, 4, 24 and 48 hours post injection*

Organ	2 hours	4 hours	24 hours	48 hours
Blood	0·02 ± 0·00	0·00 ± 0·00	0·00 ± 0·00	0·00 ± 0·00
Heart	0·00 ± 0·00	0·16 ± 0·03	0·00 ± 0·00	0·00 ± 0·00
Kidneys	0·15 ± 0·02	0·13 ± 0·03	0·10 ± 0·01	0·03 ± 0·00
Spleen	0·02 ± 0·00	0·08 ± 0·01	0·05 ± 0·00	0·00 ± 0·00
Stomach	0·02 ± 0·00	0·05 ± 0·01	0·01 ± 0·00	0·00 ± 0·00
Large intestine	0·09 ± 0·02	0·42 ± 0·08	0·01 ± 0·00	0·00 ± 0·00
Small intestine	0·05 ± 0·01	0·09 ± 0·01	0·00 ± 0·00	0·00 ± 0·00
Bone	0·67 ± 0·04	1·17 ± 0·07	1·81 ± 0·05	0·91 ± 0·08
Muscle	0·00 ± 0·00	0·10 ± 0·00	0·00 ± 0·00	0·00 ± 0·00
Lung	0·02 ± 0·00	0·15 ± 0·00	0·01 ± 0·00	0·00 ± 0·00
Liver	0·09 ± 0·01	0·11 ± 0·02	0·09 ± 0·01	0·03 ± 0·00

Table 4. *Percentage of injected dose per gram (ID/g %) after intravenous administration of 5·55 MBq ^{153}Sm-TTHMP in Syrian rat tissues at 2, 4, 24 and 48 hours post injection*

Organ	2 hours	4 hours	24 hours	48 hours
Blood	0·09 ± 0·01	0·07 ± 0·01	0·01 ± 0·00	0·00 ± 0·00
Heart	0·11 ± 0·02	0·09 ± 0·01	0·06 ± 0·01	0·04 ± 0·00
Kidneys	1·10 ± 0·12	0·93 ± 0·08	0·72 ± 0·08	0·36 ± 0·06
Spleen	0·14 ± 0·01	0·16 ± 0·02	0·06 ± 0·00	0·05 ± 0·00
Stomach	0·25 ± 0·02	0·22 ± 0·03	0·16 ± 0·01	0·17 ± 0·01
Large intestine	0·11 ± 0·01	0·28 ± 0·03	0·23 ± 0·05	0·26 ± 0·03
Small intestine	0·14 ± 0·01	0·19 ± 0·01	0·12 ± 0·02	0·09 ± 0·00
Bone	1·06 ± 0·09	1·02 ± 0·07	0·76 ± 0·09	0·57 ± 0·04
Muscle	0·05 ± 0·01	0·05 ± 0·00	0·03 ± 0·00	0·02 ± 0·00
Lung	0·17 ± 0·01	0·16 ± 0·00	0·11 ± 0·00	0·07 ± 0·01
Liver	0·16 ± 0·01	0·23 ± 0·02	0·17 ± 0·00	0·16 ± 0·01

main organ sources of the rats for ^{153}Sm-TTHMP and ^{153}Sm-PDTMP are shown in Figures 2 and 3, respectively.

Dosimetric studies

The importance of an ideal radiopharmaceutical lies in the accumulation of the complex in the

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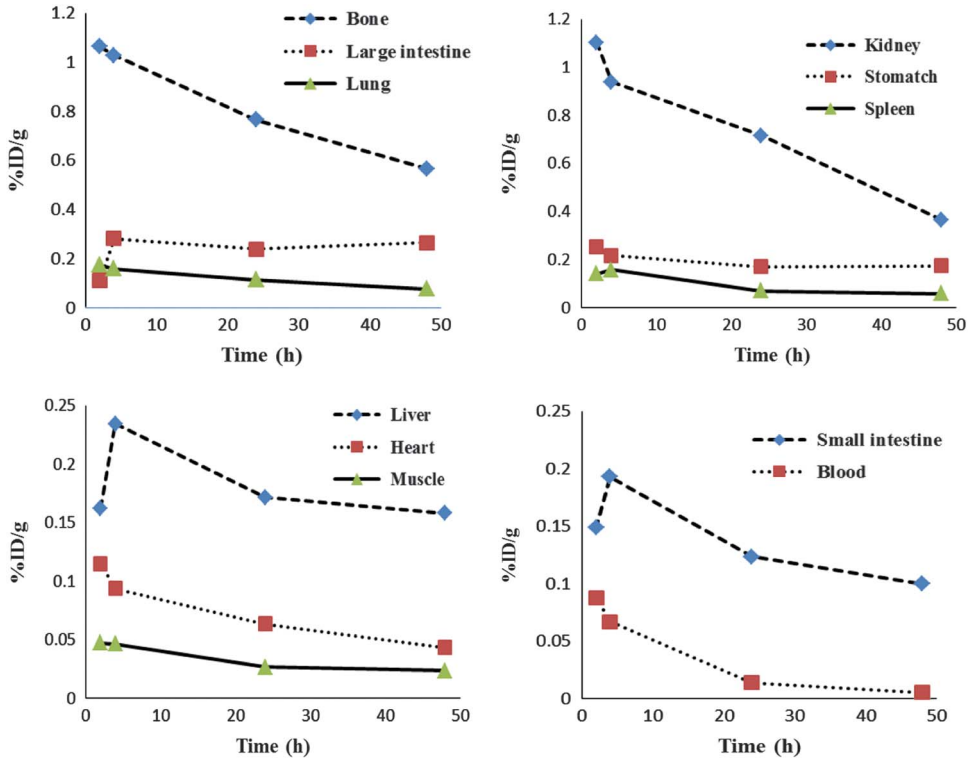

Figure 2. Non-decay corrected clearance curves for each organ of Syrian rats after injection of 5·55 MBq ^{153}Sm-TTHMP.

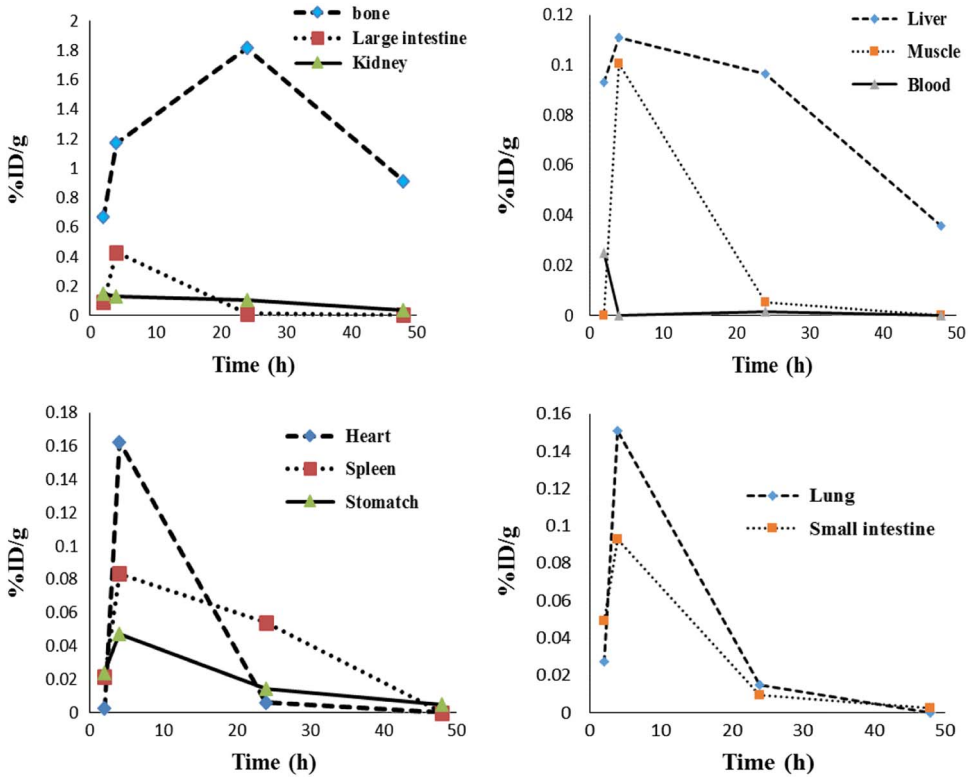

Figure 3. Non-decay corrected clearance curves for each organ of Syrian rats after injection of 5·55 MBq ^{153}Sm-PDTMP.

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target organs compared with the critical organs. Due to the high radio-sensitivity of hemato-poietic cells within the marrow of the trabecular bone cavities, the bone marrow is an absolutely main critical organ for metastatic bone pain palliation therapy.[17] Therefore, for bone-seeking radiopharmaceuticals, the dose delivered to the bone marrow is one of the most important parameters that should be considered.

Dosimetric evaluation in human organs was carried out by the RADAR method based on biodistribution data in the rat organs. The absorbed dose in human organs after the injection of these complexes is presented in Table 5. The highest absorbed dose for ^{153}Sm-TTHMP and ^{153}Sm-PDTMP is observed in the trabecular bone with 1·085 and 1·826 mGy/MBq, respectively.

Since ^{153}Sm-EDTMP is the most clinically used Sm-153 bone pain palliative radio-pharmaceutical, the average bone/red marrow dose ratio after injection of these bone-seeking agents is compared with this value for ^{153}Sm-EDTMP (Table 6). This ratio, as the target/critical organ dose ratio for these two complexes is approximately the same as ^{153}Sm-EDTMP.

The dose ratio of the trabecular bone to the other critical tissue for ^{153}Sm-TTHMP and ^{153}Sm-PDTMP is compared in Table 7. The dose ratio of the trabecular bone to the other critical tissue for ^{153}Sm-PDTMP is truly greater than ^{153}Sm-TTHMP. This suggests that ^{153}Sm-PDTMP has negligible undesirable uptake and therefore, it is a more appropriate agent for the bone pain palliation.

CONCLUSION

^{153}Sm-TTHMP and ^{153}Sm-PDTMP were prepared in high radiochemical purity (>99%, ITLC). The end products of complexes were administered to the Syrian rats and the bio-distribution of the complexes was checked 2–48 hours post injection, showing a basic process of accumulation in the bone tissue. Contrary to the bone tissues, all of the rest received almost an insignificant absorbed dose. The bone/red marrow dose ratio for these two complexes is approximately the same as ^{153}Sm-EDTMP. ^{153}Sm-PDTMP indicated lesser undesirable

Table 5. *The absorbed dose in each human organ after injection of ^{153}Sm-PDTMP and ^{153}Sm-TTHMP*

Tissue	Absorbed dose (mGy/MBq) ^{153}Sm-PDTMP	Absorbed dose (mGy/MBq) ^{153}Sm-TTHMP
Lower large intestine	0·081	0·375
Small intestine	0·012	0·059
Stomach	0·005	0·023
Heart	0·013	0·024
Kidneys	0·023	0·145
Liver	0·026	0·068
Lungs	0·015	0·044
Muscle	0·016	0·017
Red marrow	0·633	0·377
Cortical bone	1·552	0·922
Trabecular bone	1·826	1·085
Spleen	0·012	0·031
Total body	0·131	0·086

Table 7. *Trabecular bone to other critical tissue dose ratio for ^{153}Sm-TTHMP and ^{153}Sm-PDTMP*

Tissue	^{153}Sm-PDTMP	^{153}Sm-TTHMP
Kidneys	79·4	7·5
Liver	70·2	15·9
Lungs	121·7	24·7
Spleen	152·2	35·0
Total body	13·9	12·6

Table 6. *The average bone/red marrow dose ratio after injection of ^{153}Sm-EDTMP, ^{153}Sm-TTHMP and ^{153}Sm-PDTMP*

	(Cortical bone/RM) (mGy/MBq)	(Trabecular bone/RM)) (mGy/MBq)	Reference
^{153}Sm-EDTMP	(3·85/1·50) = 2·57	(4·42/1·50) = 2·95	Bevelacqua [16a]
^{153}Sm-PDTMP	(1·522/0·633) = 2·40	(1·826/0·633) = 2·88	This work
^{153}Sm-TTHMP	(0·922/0·377) = 2·44	(1·085/0·377) = 2·87	This work

[a]The data are the average of the absorbed dose for 27 independent measurements after ^{153}Sm-EDTMP injection to patients with skeletal metastases.

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uptake compared with ^{153}Sm-TTHMP. The results showed that these bone-seeking agents, especially ^{153}Sm-PDTMP, have outstanding characteristics in comparison with ^{153}Sm-EDTMP, the most clinically used bone pain palliative radiopharmaceutical and therefore can be good candidates for the bone pain palliation in the patients with the bone metastasis. According to the threshold amount of the absorbed dose for the critical organs, the obtained results can be useful for the determination of the maximum permissible injected activity of these radiopharmaceuticals for radiotherapy of the bone metastases in the treatment planning programs.

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