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ORIGINAL RESEARCH ARTICLE

Radiation absorbed dose evaluation of [^{153}Sm]Sm-DOTMP radiopharmaceutical based on biodistribution data in Wistar rats

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ABSTRACT

Introduction: Bone metastases are a frequent complication in various tumors such as prostate, breast, and lung carcinoma often causing progressive pain. Bone-seeking beta-emitting radiopharmaceuticals such as samarium-153-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid ([^{153}Sm]Sm-DOTMP) are potentially utilized for bone pain palliation.

Methods: This research evaluated the radiation absorbed dose of [^{153}Sm]Sm-DOTMP radiopharmaceutical for adult men based on biodistribution data in Wistar rats. The Medical Internal Radiation Dosimetry (MIRD) dose calculation method and the Sparks and Aydogan methodology were applied.

Results: About 56% of the injected activity is accumulated on the surface of the trabecular and compact bones. Radiation absorbed doses of red bone marrow and osteogenic cells were estimated at 0.66±0.04 and 3.43±0.23 mGy/MBq, respectively. The maximum administrated activity was obtained at 43.3 MBq/kg (1.17 mCi/kg) of body weight with about 10.4 Gy absorbed dose of bone surface for a 70 kg adult man. The effective dose of [^{153}Sm]Sm-DOTMP radiopharmaceutical was estimated at 0.14±0.01 mSv/MBq and the urinary bladder wall and kidneys absorbed doses were evaluated at about 0.20±0.02 mGy/MBq and 0.05±0.01 mGy/MBq, respectively. The urinary and gastrointestinal tracts were the next organs with the highest radiation absorbed dose as the main routes of excretion of radioactivity.

Conclusion: This study showed that the radiopharmaceutical [^{153}Sm]Sm-DOTMP can provide palliative care for bone metastases while delivering low undesired doses to surrounding normal tissues.

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INTRODUCTION

Bone metastases are developed in the advanced stage of patients suffering from breast, lung, and prostate solid malignant tumors [1]. These skeletal metastatic lesions often result in excruciating pain, immobility, depression, neurological deficits, and hypercalcemia [2, 3]. Various bone-seeking beta emitting radiopharmaceuticals such as strontium-89-dichloride ([^{89}Sr]$SrCl_2$), samarium-153-ethylenediaminetetramethylene phosphonic acid ([^{153}Sm]Sm-EDTMP), holmium-166-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid ([^{166}Ho]Ho-DOTMP), renium-188-1-hydroxyethyllidenediphosphaonate ([^{188}Re]Re-HEDP), renium-186-1-hydroxyethyllidenediphosphaonate ([^{186}Re]Re-HEDP), ([^{177}Lu]Lu-DOTMP) and lutetium-177-ethylenediaminetetramethylene phosphonic acid ([^{177}Lu]Lu-EDTMP) are effectively utilized for bone pain palliation, resulting in significant improvement in the quality of life of patients suffering from bone pain [1, 4-8].

Samarium-153 radionuclide with 46.27-hour half-life, four main medium energy beta particles (808.20 keV [17.5%], 710.77 keV [0.4%], 705.02 keV [49.6%] and 635.35 keV [32.2%]) and gamma rays for imaging studies (103.18 keV [30.0%] and 69.67 keV [4.9%]) is an excellent theranostic radiotracer which is recently used for radionuclide therapy [5]. This radionuclide is the most widely used pain palliation radiopharmaceutical agent in the United States [6]. It can be attached to phosphonic acid ligands which have been identified to have in vivo localization and clearance properties, these are nearly ideal for radionuclide therapy in patients with metastatic bone cancers [7]. Samarium-153 radionuclide has a high thermal neutron capture cross-section through the ^{152}Sm(n,γ)^{153}Sm production route [8]. Acyclic and cyclic polyaminophosphonate conjugates of samarium-153 radionuclide have been used in human and normal animal studies for bone pain palliation purposes, including [^{153}Sm]Sm-EDTMP and [^{153}Sm] Sm-DOTMP radiopharmaceuticals [9]. Commercially known as Quadramet, [^{153}Sm] Sm-EDTMP is the most widely used radiopharmaceutical for metastatic bone pain palliation, and it was approved by the Food and Drug Administration (FDA) of USA in 1997 [7-9].

Samarium forms a very stable complex with the DOTMP ligand and hence [^{153}Sm]Sm-DOTMP is also one of the potential radiopharmaceuticals for bone pain palliation [10]. DOTMP can be prepared with a much lower ligand concentration as compared to the acyclic ligand EDTMP. Hence, the low specific activity of samarium-153 will suffice for the preparation of [^{153}Sm]Sm-DOTMP [11]. [^{153}Sm]Sm-DOTMP is under commercial development under the trade name 'CycloSam'. It uses a 3:1 ligand to metal ratio. However, [^{153}Sm]Sm-EDTMP requires a 300:1 ligand to metal ratio to ensure the samarium remains chelated to EDTMP. CycloSam localizes only in bone with almost no uptake elsewhere in the body and it clears quickly through the renal system [10-12]. The four amine groups available in 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) ligands compared to the two amine groups in ethylenediaminetetramethylene phosphonic acid (EDTMP) results in better complexation properties. The DOTMP agent can be prepared at the hospital radiopharmacy following simple procedures through a wet chemistry method or by using a freeze-dried DOTMP kit [11, 13].

Some investigations concerned the production, purity assessment, formulation, biodistribution, and toxicity studies of [^{153}Sm]Sm-DOTMP radiopharmaceuticals. Chakraborty et al. prepared and biologically evaluated the [^{153}Sm]Sm-DOTMP as a potential agent for bone pain palliation using the DOTMP ligand provided in situ [14]. The tissues and the organs of Wistar rats were excised at 30 min, 1 h, 3 h, 24 h, and 48 h post-anesthesia and the distribution of the activity in different organs was calculated. Systemic toxicity of [^{153}Sm]Sm-DOTMP radiopharmaceutical was studied through intravenous injection of equivalent skeletal doses to normal dogs [12]. Das et al. prepared the clinical-scale [^{153}Sm]Sm-DOTMP radiopharmaceutical using a freeze-dried DOTMP kit [11]. Biological evaluation was studied at 3 h, 1 d, and 2 d post-anesthesia on Wistar rats.

To determine the recommended doses of recently developed radiopharmaceuticals for humans, it is necessary to conduct dosimetric studies in the animal body (preclinical) and to generalize the results to humans. The dosimetric studies of [^{153}Sm]Sm-DOTMP radiopharmaceutical for some animals (Sprague-Dawley and Wistar rats) have been reported in some articles [15, 16]. Simón et al. conducted a preclinical investigation on the dosimetric study of [^{153}Sm]Sm-DOTMP as a bone-seeking radiopharmaceutical [15]. The dosimetric studies were performed using male Sprague–Dawley rats and residence times of source organs were measured in rats and extrapolated to human beings. Then source organs' residence times were entered into the OLINDA/EXM 1.1 software to

calculate target organ doses for the 73.7 kg adult male model. The same group implicated the human internal dosimetry of the potential radionuclidic impurities in [^{153}Sm]Sm-DOTMP radiopharmaceutical from preclinical data using Sprague-Dawley rats [16].

There is currently a lack of comprehensive preclinical and clinical studies on the biokinetics and dosimetry of this radiopharmaceutical in human. While the biodistribution of radiopharmaceuticals in humans is crucial for assessing absorbed doses with nuclear medicine imaging equipment, this research aims to estimate the radiation absorbed dose from [^{153}Sm]Sm-DOTMP radiopharmaceutical to humans for the first time. This estimation is based on previously published biodistribution data in Wistar rats [14]. In addition, the maximum administrated activity of [^{153}Sm]Sm-DOTMP radiopharmaceutical is suggested per one-kilogram body weight of an adult man. The effective dose of this radiopharmaceutical is estimated, subsequently, and the activity corresponding to the maximum tolerated dose (MTD) on bone and bone marrow tissues will be calculated. Wherever possible, the result will be compared with other published data from the literature regarding bone pain palliative agents.

METHODS

Biodistribution studies of [^{153}Sm]Sm-DOTMP in Wistar rats

Production and quality control of [^{153}Sm]Sm-DOTMP radiopharmaceutical has been fully described by Chakraborty et al. [14]. In this research, biodistribution data in Wistar rats from the aforementioned articles are used for radiation dose estimates of [^{153}Sm]Sm-DOTMP radiopharmaceutical in man. Briefly, the radiolabeled DOTMP agent with carrier-added samarium-153 radionuclide was produced by irradiation of natural Sm_2O_3 (26.7% ^{153}Sm) at a thermal neutron flux of 3×10^{13} n cm^{-2} s for a period of 7 d. Biodistribution of [^{153}Sm]Sm-DOTMP was studied in normal Wistar rats injected with 0.15–0.2 ml (3–4 MBq) of radioactive solution through their tail vein. The animals were sacrificed post-anesthesia at 30 min, 1 h, 3 h, 24 h, and 48 h post-injection. Three rats were sacrificed at each time interval and organs were weighed and counted in a flat-type NaI(Tl) scintillation counter. Distribution of the activity in different organs was calculated as the percent of injected activity per gram of organ (%ID/g Organ). The percent of injected activity in animal organs (%IA/organ) was calculated by multiplying of %ID/g of each organ by its weight in turn. The weight of selected organs of the adult man and normal Wistar rats is given in Table 1 [17-19].

Biodistribution studies of [^{153}Sm]Sm-DOTMP in humans

The percent of injected activity (%IA) in human organs is extrapolated from the percent of injected activity (%IA) in animal organs for adaptation of the [^{153}Sm]Sm-DOTMP radiopharmaceutical biodistribution pattern between rats and humans. For this purpose, the well-known Sparks and Aydogan model is applied in this study to have a rough approximation of the radiation absorbed dose in man from [^{153}Sm]Sm-DOTMP radiopharmaceutical [20]. Based on this method, the percent of injected activity (%IA) in human organs is calculated as follows:

$$\%\text{IA Human organ} = \%\text{IA Animal organ} \times \frac{\frac{\text{Organ mass}_{\text{human}}}{\text{Body mass}_{\text{human}}}}{\frac{\text{Organ mass}_{\text{animal}}}{\text{Body mass}_{\text{animal}}}} \quad (1)$$

In addition, the activity of each organ after injection of A_0 Bq of [^{153}Sm]Sm-DOTMP is calculated from the following equation, and the time-activity curves are produced according to this equation:

$$A(t) = \frac{\%IA(t)}{100} \times A_0 e^{-\lambda t} \quad (2)$$

Dosimetric calculations

The radiation absorbed doses of target organs were estimated using methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine [21]. The calculations are based on the methodology described below:

$$D(r_T) = \sum_{r_s} \tilde{A}(r_S) S(r_T \leftarrow r_S) \quad (3)$$

Where, $D(r_T)$ stated in (mGy) is the radiation absorbed dose to a target organ, r_T, from source organs, r_S. $\tilde{A}(r_S)$ is the accumulated activity in the source organ, r_S, which is calculated by the following equation:

$$\tilde{A}(r_S) = \int_0^\infty A(r_S, t)\, dt \quad (4)$$

The $S(r_T \leftarrow r_S)$ expressed in [mGy/(MBq s^{-1})], is the specific absorbed fraction of energy for the target organ, r_T, per unit accumulated activity in the source organ, r_S. The S-values of adult man for samarium-153 radionuclide are taken from the OLINDA/EXM version 1.0 (Organ Level INternal Dose Assessment/Exponential Modeling) software [22]. About 13 tissues were considered as source organs, and their S-values were applied for radiation absorbed dose calculations of about 22 organs.

Table 1. Weight of selected organs of the adult man and Wistar rat

Human		Wistar rat	
Organ	**Weight (g)**	**Organ**	**Weight (g)**
Total body	70000	Total body	190
Heart, without blood in chambers	330	Heart	0.7
Kidneys (both)	310	Kidneys (both)	1.5
Stomach	150 Wall; 250 contents	Stomach	1.0 wall
Small intestine	640 Wall; 400 contents	Small bowel	1.9 wall
Muscle, skeletal	28000	Muscle	73.7
Lungs, including blood	1000	Lungs	1.2
Liver	1800	Liver	8.1
Upper large intestine (ULI)	210 Wall; 220 contents	Cecum	0.6 wall
Lower large intestine (LLI)	160 Wall; 135 contents	Colon	1.0 wall
Spleen	180	Spleen	0.7
Cortical (compact) bone	4000	Bone	13.3
Trabecular (cancellous) bone	1000	Brain	1.8
Reference	[17]	Reference	[18, 19]

The accumulated activity (total number of disintegrations) of each source organ was calculated in two steps. In the first step, due to the availability of biodistribution data up to 48 h post-injection, the time-activity curve of each source organ was integrated up to 48 h (2 days), and the area under the curve was considered as the accumulated activity until 48 h. In the second step, one mono-exponential function was considered as the rest of the time-activity curve from 48 h to infinity. Then it was integrated to infinity and the area under the curve was reported as the second part of the accumulated activity of each source organ. The time-activity curves after 48 h were considered mono-exponential functions due to this rational assumption that organs' activities decrease with radioactive decay and biological elimination of the radionuclide in that organ (i.e. with the effective half-life of each organ). Therefore, the exponent of any mono-exponential function represents the effective half-life of each organ. Four last time intervals (1 h, 3 h, 24 h, and, 48 h, except 0.5 h) were used for fitting mono-exponential functions to the time-activity curves of most source organs after 48 h.

In addition, the effective dose was calculated according to the latest recommendations of the ICRP publication 103 [23], and was calculated from the following equation:

$$E = \sum_T w_T \, H(r_T) \quad (5)$$

Where w_T is the weighting factor for tissue or organ T and H_T, is the equivalent dose in tissue T, given in Sv. The weighting factors for tissues are given in Table 2 [23].

Table 2. Tissue weighting factors, W_T, in the 2007 recommendations of ICRP, publication 103 [23]

Organ/Tissue	Number of tissues	W_T	Total contribution
Lung, stomach, colon, bone marrow, breast, remainder	6	0.12	0.72
Gonads	1	0.08	0.08
Thyroid, esophagus, bladder, liver	4	0.04	0.16
Bone surface, skin, brain, salivary glands	4	0.01	0.04

RESULTS

Biodistribution studies of [^{153}Sm]Sm-DOTMP in Wistar rats and humans

The biodistribution of [^{153}Sm]Sm-DOTMP radiopharmaceutical in different organs of Wistar rats is given in Figure 1 according to Chakraborty et al. study [14]. The uncertainties are given in terms of one standard deviation.

As shown in Figure 1, the [^{153}Sm]Sm-DOTMP radiopharmaceutical has fast blood clearance after 30 min and is excreted via the urinary tract (kidney). The radioactivity was mainly located in the liver, kidney, and bone. It is preferentially localized in the osteoblastic lesions.

The extrapolated %IA/organs for humans is given in Figure 2. The uncertainties are given in terms of one standard deviation, too. As shown in Figure 2, most of the activity is accumulated in bone tissue, similar to the Wistar rat biodistribution pattern.

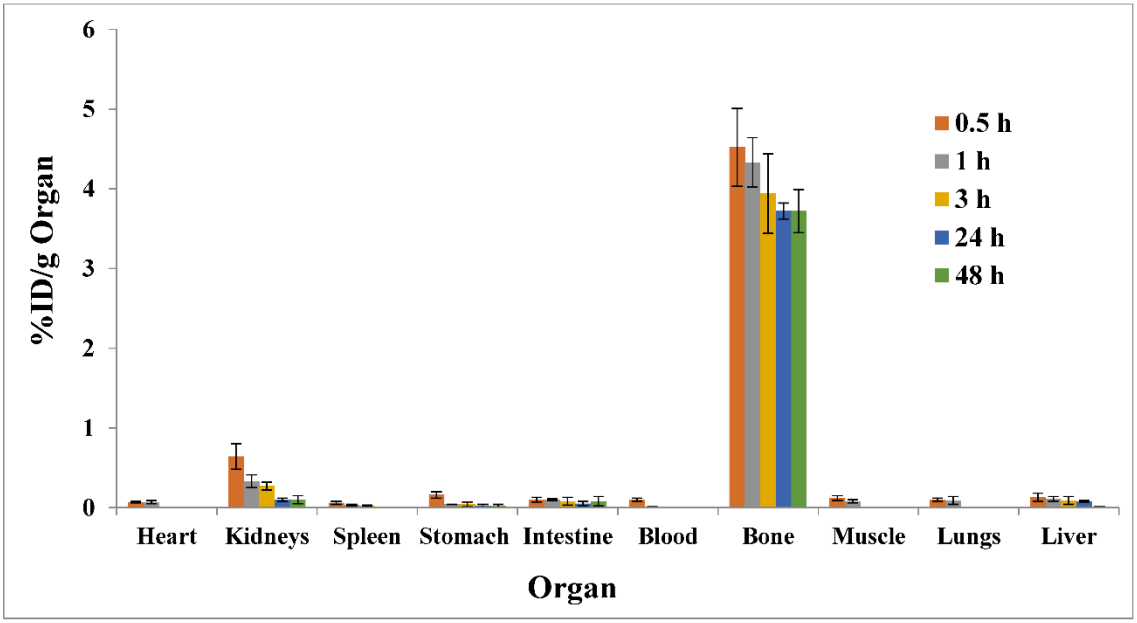

Figure 1. Percentage of the injected activity per organ (%IA/organ) of [^{153}Sm]Sm-DOTMP in normal Wistar rats [14]

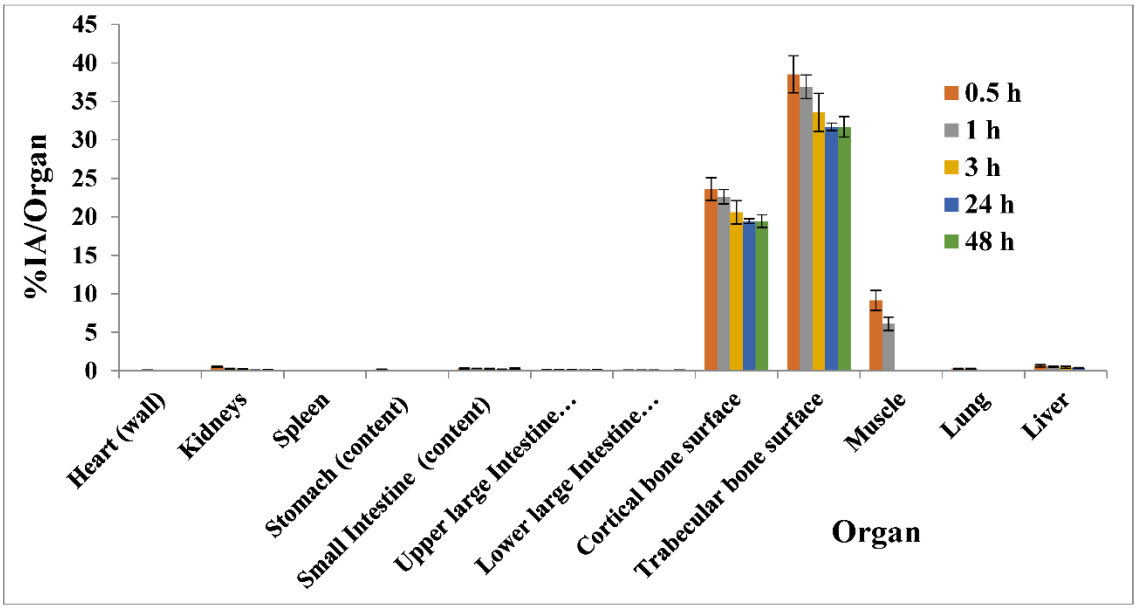

Figure 2. Percentage of the injected activity per organ (%IA/organ) of [^{153}Sm]Sm-DOTMP in the adult man organs

Human bone surface uptake was considered as the trabecular (cancellous) and the cortical (compact) bones' surface proportion. The trabecular and the cortical bones consist of 62% and 38% of the total skeletal surface, respectively [24]. Figure 2 shows that about 56% of the injected activity is accumulated on the surface of the trabecular and compact bones. This ligand has lower retention in the muscle, liver, kidneys, and small intestine tissues compared to bone tissue in the first-time intervals post-injection (Figure 2). The large weight fraction of muscle in the human body (about 40% of total body weight) and the major excretion route of this radiopharmaceutical through urinary and gastrointestinal tracts are the main reasons for this activity accumulation. The

%IA in the remaining source organs was less than 0.18% after 48 h post-injection.

The time-activity curves for source organs of humans are given in Figure 3 a and b per injection of 1MBq of [^{153}Sm]Sm-DOTMP radiopharmaceutical. As shown in Figure 3, most of the activity is rapidly deposited on cortical and trabecular bone surfaces (about 0.23 and 0.38 MBq at 30 min post-injection, respectively). Approximately, after 1 half-life of samarium-153 radionuclide, there are insignificant activities in organs except for bone tissue.

More than 40% of the injected activity would be excreted through the urinary tract in the first hours post-injection. Therefore, the urinary bladder wall absorbed dose and its content's delivered dose to other organs should not be forgotten. Unfortunately, Chakraborty et al. did not report the %IA of the urinary bladder wall and its content [14]. To make an approximate estimation, accumulated urinary excretion data of a similar radiopharmaceutical for humans [25] was employed for radiation absorbed dose calculation of the urinary bladder wall. In this article [25], fractionated urine samples were collected over the first 48 hours post-injection of radiopharmaceutical for humans.

The frequency of urination and the activity of each urination should be known for the precise absorbed dose estimation of the urinary bladder wall. Conservatively, the 4, 8, 24, and 48 h time points were considered as the number of bladder evacuations. The bladder activity is considered zero after any depletion. The time-activity curve for the urinary bladder content per injection of 1 MBq of [^{153}Sm]Sm-DOTMP is given in Figure 3b as well.

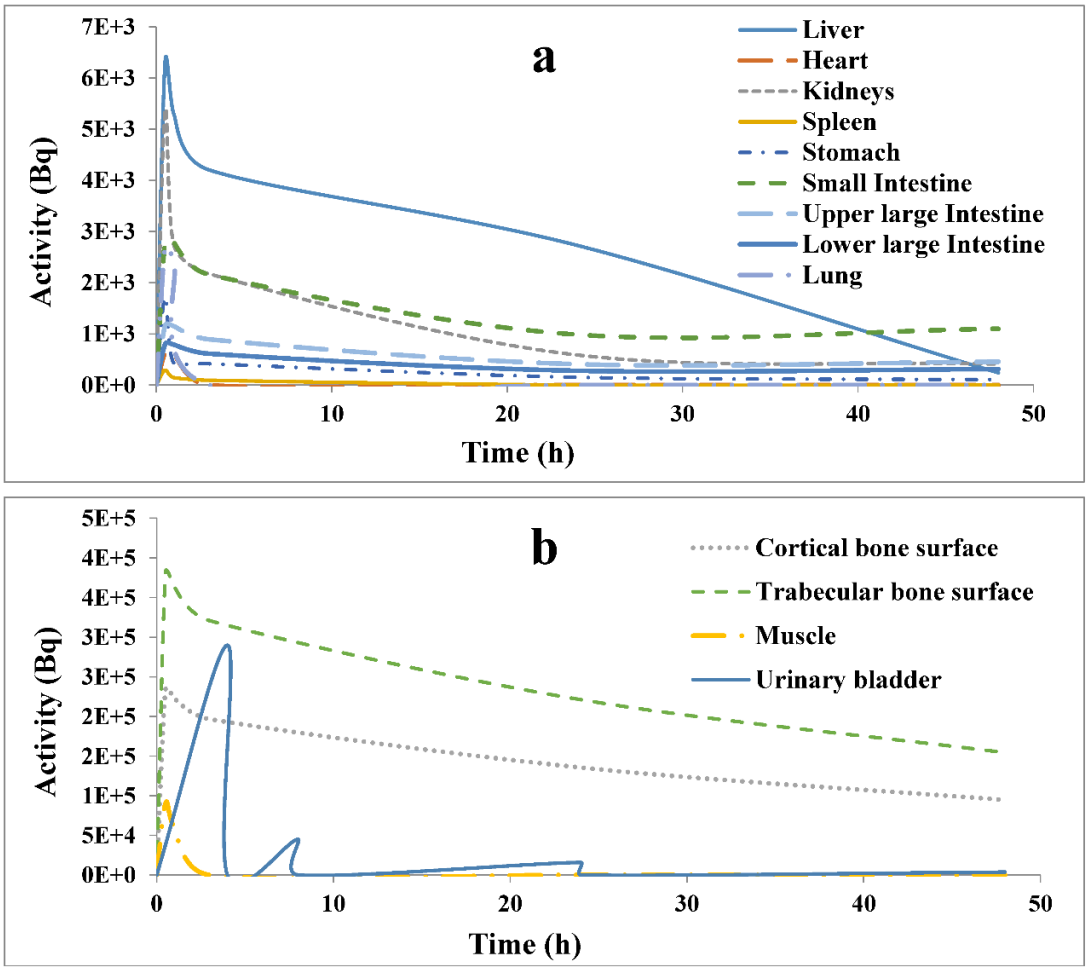

Figure 3. The time-activity curves of [^{153}Sm]Sm-DOTMP for source organs of the adult man

Radiation absorbed dose calculations

The accumulated activities in the source organs of the adult man per injection of 1 MBq of the [^{153}Sm]Sm-DOTMP radiopharmaceutical are given in Table 3. The uncertainties of accumulated activities are given in terms of one standard deviation. In addition, estimated effective half-lives of source organs are given in this Table.

As expected, the highest accumulated activity of [^{153}Sm]Sm-DOTMP radiopharmaceutical is observed in trabecular and cortical bone surfaces. This radiopharmaceutical was removed from this tissue with an effective half-life of 37.8 h. Removal of this radiopharmaceutical from bone tissue was approximately with a radiological half-life of samarium-153 radionuclide (T_R=46.27 h), indicating strong adhesion of this radiopharmaceutical on bone surface. The biological half-life of [^{153}Sm]Sm-DOTMP radiopharmaceutical on bone tissue was calculated about 207 h. Due to the fast excretion of [^{153}Sm]Sm-DOTMP through the urinary tract, the urinary bladder has the greatest accumulated activity after the bone tissue.

Figure 4 shows a mono-exponential function fitted to the time-activity curve of the cortical bone tissue to extract the effective decay constant (effective half-life) for this source organ. As shown in Figure 4, the effective decay constant was extrapolated to about 0.01833 h^{-1} (The effective half-life = 37.8 h) for bone tissue with an R-squared value close to 1.

Evaluated radiation absorbed doses of an adult man per injection of 1 MBq [^{153}Sm]Sm-DOTMP radiopharmaceutical activity are given in Table 4. The uncertainties of radiation absorbed doses are given in terms of one standard deviation. The highest radiation absorbed dose was calculated for skeletal tissue (Osteogenic cells and red bone marrow). Red bone marrow and osteogenic cells' radiation absorbed doses were estimated at 0.66±0.04 and 3.43±0.23 mGy/MBq, respectively.

Table 3. The accumulated activities (MBq s) and the effective half-lives (h) of the source organs for an adult man per injection of 1 MBq of [^{153}Sm]Sm-DOTMP

Source organ	Accumulated activity	Effective half-life (h)
Heart	3.9±0.2	0.25
Kidneys	207.9±33.1	14.44
Stomach contents	47.8±16.6	15.90
Small intestine contents	421.6±115.6	32.80
Upper large intestine (ULI) contents	174.4±47.8	32.80
Lower large intestine (LLI) contents	119.7±32.8	32.80
Spleen	5.0±0.7	3.06
Cortical bone surface	43221.5±2028.1	37.81
Trabecular bone surface	70519.3±3309.0	37.81
Muscle	432.5±25.0	0.14
Lungs	15.7±1.4	0.21
Liver	454.3±70.2	11.15
Urinary bladder content	3020.6±241.6	---

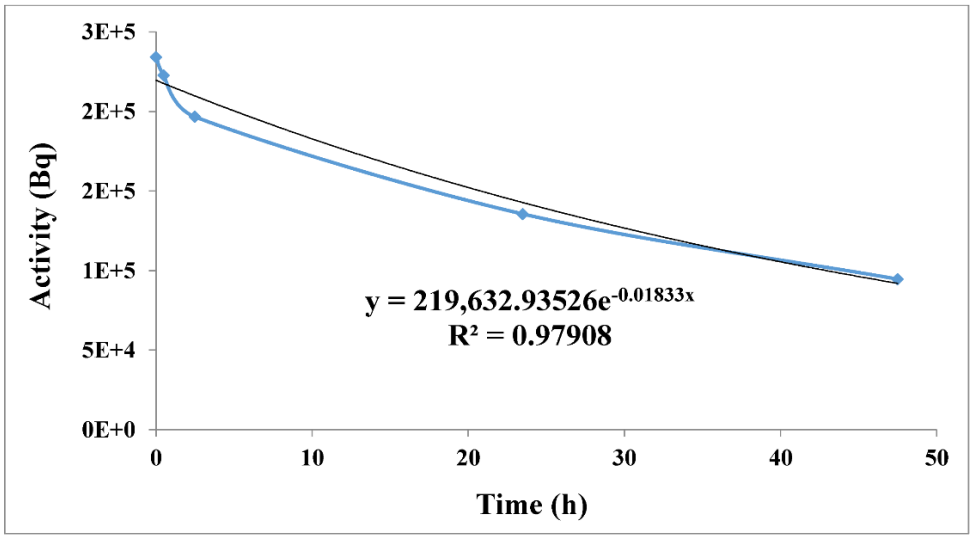

Figure 4. Fitting mono-exponential function to the time-activity curve of the cortical bone tissue

Table 4. The radiation absorbed doses (mGy/MBq) of the adult man's target organs per injection of 1 MBq of [153Sm]Sm-DOTMP radiopharmaceutical

Target organs	Our study	Simón et al. [15]
Adrenal	0.006±0.001	0.007
Brain	0.008±0.000	0.009
Breasts	0.002±0.000	0.002
Gallbladder wall	0.003±0.000	0.003
Lower large intestine (LLI) wall	0.024±0.004	0.048
Small intestine	0.025±0.004	0.030
Stomach wall	0.006±0.001	0.014
Upper large intestine (ULI) wall	0.020±0.003	0.030
Heart wall	0.004±0.000	0.004
Kidneys	0.034±0.004	0.075
Liver	0.013±0.001	0.013
Lungs	0.005±0.000	0.006
Muscle	0.005±0.000	0.006
Pancreas	0.004±0.000	0.004
Red marrow	0.660±0.044	0.755
Osteogenic cells	3.433±0.230	3.930
Skin	0.003±0.000	0.003
Spleen	0.004±0.000	0.005
Testes	0.002±0.000	0.003
Thymus	0.003±0.000	0.003
Thyroid	0.004±0.000	0.005
Urinary bladder wall	0.322±0.020	0.721
Total body	0.076±0.005	0.088
Effective dose (mSv/MBq)	0.142±0.007	0.177
Animal	Wistar rat	Sprague-Dawley rat
Method	MIRD, Sparks and Aydogan [20] model	Relative organ mass scaling, OLINDA/EXM

The urinary and gastrointestinal tracts are the next organs with the highest radiation absorbed dose (about 0.32±0.02 mGy/MBq, 0.03±0.00 mGy/MBq, and 0.03±0.00 mGy/MBq for the urinary bladder wall, kidneys, and, small intestine respectively), demonstrating rapid clearance of

the radiopharmaceutical from the blood circulation through the urinary and gastrointestinal tracts. As shown in Table 4, the effective dose of [^{153}Sm]Sm-DOTMP radiopharmaceutical (0.14±0.01 mSv/MBq) was obtained lower than [^{177}Lu]Lu-EDTMP (0.26 mSv/MBq) [6], [^{177}Lu]Lu-DOTMP (0.19 mSv/MBq) [26], [^{166}Ho]Ho-EDTMP (0.29 mSv/MBq) and ^{153}Sm-EDTMP (0.21 mSv/MBq) radiopharmaceuticals [27].

Simón et al. radiation absorbed dose estimation of human organs from [^{153}Sm]Sm-DOTMP is also given in Table 4 for comparison as the only preclinical available data [15]. As shown in Table 4, the evaluated radiation absorbed doses of different tissues are close to each other for both of the studied rat races (Sprague-Dawley and Wistar).

In Table 5, the maximum tolerated doses (MTD) of bone and bone marrow tissues are given in terms of GBq. The MTD values for the aforementioned tissues are about 50–70 and 1–2 Gy, respectively [28]. Radiation absorbed dose of 25 Gy to the red bone marrow can be considered as the ablative therapeutic dose for this tissue [29, 30]. In addition, the maximum activity to be administered to patients in terms of MBq/kg of body weight is given in Table 5. For calculation of the last quantity, the maximum tolerated dose to the red bone marrow was supposed for about 2 Gy.

As seen in Table 5, the maximum administrated activity of [^{153}Sm]Sm-DOTMP radiopharmaceutical should not exceed 43.32 MBq/kg (1.17 mCi/kg) of body weight. This administrated activity will result in about a 10.4 Gy bone surface absorbed dose for a 70 kg adult man. Only holmium-166 compounds ([^{166}Ho]Ho-EDTMP and [^{166}Ho]Ho-DOTMP) could result in complete extirpation of bone marrow, while bone tissue dose would not exceed the MTD limit. Other radiophosphonates' required activities to complete red marrow ablation would exceed the MTD limit of bone tissue. So [^{153}Sm]Sm-DOTMP radiopharmaceutical would not be appropriate for bone marrow ablation. Samarium-153 radiopharmaceuticals ([^{153}Sm]Sm-EDTMP and [^{153}Sm]Sm-DOTMP) approximately deliver the same radiation absorbed doses to bone marrow. However, it should be noted that [^{153}Sm]Sm-EDTMP delivers a higher dose to the bone surface compared with [^{153}Sm]Sm-DOTMP radiopharmaceutical. This is due to the relatively high bone uptake property of the EDTMP ligand (up to 70%) relative to the DOTMP ligand (up to 56%) [14, 31].

DISCUSSION

[^{153}Sm]Sm-DOTMP radiopharmaceutical showed significant accumulation (up to 56%) in the cortical and trabecular bone surfaces, and almost no significant uptake was observed in soft tissue or any other major non-target organs after 1 day. This complex was rapidly cleaned of blood circulation and the main route of excretion was urinary and gastrointestinal tracts.

Radiolabeled phosphonates such as [^{153}Sm]Sm-EDTMP and [^{153}Sm]Sm-DOTMP radiopharmaceuticals, mainly tend to be localized uniformly on cortical and trabecular bone surfaces [28, 31]. Most of the distributed activity on bone tissue was deposited on the trabecular bone surface because of the larger surface area of trabecular bone against the cortical one (10.5 m^2 vs. 6.5 m^2) [24]. Due to the strong adhesive property of the DOTMP agent on bone tissue, the biological elimination of this radiopharmaceutical from bone tissue can be disregarded and the effective half-life (38 h) was comparable with the radiological half-life of samarium-153 radionuclide (46 h).

The bone tissue receives a more radiation absorbed dose from samarium-153 compared to bone marrow (3.43±0.23 vs. 0.66±0.04 mGy/MBq). It can be said that those radiopharmaceuticals whose bone marrow to bone tissue absorbed dose ratio is less than 40% are suitable for bone pain palliation purposes (Table 5).

The medium-energy beta particles and low-energy gamma rays of samarium-153 radionuclide, in comparison to relative to high-energy beta particles of holmium-166 and relatively higher energy and branching ratio gamma rays of lutetium-177 radionuclides are responsible for the lower comparable effective dose of [^{153}Sm]Sm-DOTMP radiopharmaceuticals. The [^{153}Sm]Sm-DOTMP has slightly faster blood clearance and lower retention in the liver and kidneys compared to [^{153}Sm]Sm-EDTMP radiopharmaceutical [7, 13, 14].

Although the extrapolation between nonhuman primates (such as beagles, baboons, rabbits, mice, and rats) and human data may lead to overestimation or underestimation of absorbed dose, previously published numerous articles in the literature have justified the usefulness of this method for preclinical and initial absorbed dose estimations of newly developed radiopharmaceutical [27, 32]. However, imaging studies are the principal method for the absorbed dose assessments of radiopharmaceuticals in nuclear medicine.

Table 5. The maximum tolerated doses (MTD) of bone and bone marrow for aminophosphonic acid radiopharmaceuticals

Tissue	[^{90}Y]Y-EDTMP	[^{153}Sm]Sm-EDTMP	[^{166}Ho]Ho-DOTMP	[^{166}Ho]Ho-EDTMP	[^{186}Re]Re-HEDP	[^{188}Re]Re-HEDP	[^{177}Lu]Lu-EDTMP	[^{177}Lu]Lu-DOTMP	[^{153}Sm]Sm-DOTMP
Activity (GBq) corresponding to MTD of bone (70 Gy)	3.9	16.2	77.8	22.7	22.4	18.4	11.3	13.67	20.39
Activity (GBq) corresponding to MTD of bone marrow (2 Gy)	1.1	2.9	3.9	1.4	2.2	3.3	1.9	2.3	3.03
Min. activity (GBq) required for bone marrow ablation (25 Gy)	13.9	35.7	48.4	17.4	27.2	41.0	22.7	28.2	37.90
Max. administered activity (MBq/kg)	15.7	41.4	55.7	20.1	31.4	47.1	27.1	32.2	43.32
Bone surface absorbed dose (mGy/MBq)	18	4.3	0.9	3.1	3.1	3.8	6.2	5.1	3.4
Bone marrow absorbed dose (mGy/MBq)	1.8	0.7	0.5	1.4	0.9	0.6	1.1	0.9	0.7
(Bone marrow absorbed dose/Bone surface absorbed dose) × 100	10.0	16.3	55.6	45.2	29.0	15.8	17.7	17.6	20.6
Reference	[33]	[34]	[30]	[28]	[35]	[36]	[3]	[26]	This work

CONCLUSION

The radiation absorbed dose, effective dose, effective half-lives, and accumulated activities of tissues were evaluated for [^{153}Sm]Sm-DOTMP radiopharmaceutical in adult men based on biodistribution data in Wistar rats. The results indicate that, per unit injection activity, of [^{153}Sm]Sm-DOTMP radiopharmaceutical, the osteogenic cells will receive about 5 times more radiation dose than red bone marrow. Although the bone surface absorbed doses of [^{153}Sm]Sm-DOTMP radiopharmaceutical are not comparable to those of [^{90}Y]Y-EDTMP, the delivered dose to the bone surface is similar to other clinically used samarium-153 radiopharmaceutical such as ([^{153}Sm]Sm-EDTMP). Our study provides a theoretical basis for subsequent clinical dosimetry studies of [^{153}Sm]Sm-EDTMP in patients with developed bone metastasis, helping to estimate the overall effectiveness and safety of this newly introduced radiopharmaceutical as a bone pain palliation agent.

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