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Radiation Absorbed Dose Evaluation of [^{177}Lu] Lu-DOTMP Radiopharmaceutical in Man Based On Biodistribution Data in Wistar Rats

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ABSTRACT

Introduction: Bone metastasis is the advanced stage of solid malignant tumors. Bone-avid beta-emitting radiopharmaceuticals such as lutetium-177-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid ([^{177}Lu]Lu-DOTMP) are effectively utilized for bone pain palliation. Radiation absorbed dose evaluation of such radiopharmaceuticals is needed in clinical works for estimating the risk associated with the usage of recently developed radiopharmaceuticals.

Material and Methods: The radiation absorbed dose of [^{177}Lu]Lu-DOTMP radiopharmaceutical was evaluated 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 40% of the injected activity is accumulated on the surface of the trabecular and compact bones. Radiation absorbed dose of red bone marrow and osteogenic cells were estimated at 0.89±0.07 and 5.12±0.40 mGy/MBq, respectively. The maximum administrated activity was obtained at 32.2 MBq/kg (0.87 mCi/kg) of body weight with about 11.6 Gy absorbed dose of bone surface for a 70 kg adult man. The effective dose of [^{177}Lu]Lu-DOTMP radiopharmaceutical was estimated at 0.19±0.02 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.

Conclusion: This study indicated that [^{177}Lu]Lu-DOTMP radiopharmaceutical can provide palliative care for bone metastases with low undesired doses to other 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]. Bone-avid 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].

Lutetium-177 radionuclide with a 6.73-day half-life is an excellent theranostic radiotracer which was recently used for radionuclide therapy. This radionuclide emits three beta particles (498.30 keV [78.6%], 385.35 keV [9.1%], and 176.98 keV [12.2%]) and two gamma rays (208.37 keV [11%] and 112.95 keV [6.4%]) appropriate for imaging studies [5]. The approximately longer half-life of ^{177}Lu, in comparison with ^{153}Sm, ^{166}Ho, $^{186/188}$Re, ^{165}Dy, ^{175}Yb, ^{105}Rh, ^{149}Pm, and ^{142}Pr radionuclides, provides a great advantage for delivering the radiopharmaceutical to locations far away from the radionuclide production center [6,7]. Also, lutetium-177 emits beta particles with medium energy that, due to less penetration, ensures minimal bone marrow suppression. This radionuclide has a high thermal neutron capture cross-section through the ^{176}Lu(n,γ)^{177}Lu production route [8].

Various acyclic and cyclic polyaminophosphonate conjugates of lutetium-177 radionuclide have been used in human and normal animal studies for bone pain palliation purposes, including: [^{177}Lu]Lu-CTMP

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[9], [177Lu]Lu-TTHMP [10], [177Lu]Lu-PYP [11], [177Lu]Lu-MDP [12], [177Lu]Lu-DOTA-ZOL [13], [177Lu]Lu-DOTMP [9,14-21], [177Lu]Lu-EDTMP [8,22-26], [177Lu]Lu-DOTA-TATE [26,27], [177Lu]Lu-HEDP [28] and [177Lu]Lu-DPD [28], which among them [177Lu]Lu-EDTMP and [177Lu]Lu-DOTMP are the only radiopharmaceutical of lutetium-177 radionuclide which has been clinically tested as bone pain palliation agents [8,9,14-26].

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 radiolabelling with lanthanide isotopes such as lutetium-177, samarium-153, and holmium-166 [29]. The DOTMP agent is prepared through either the wet chemistry method or a freeze-dried DOTMP kit [17, 18]. Preclinical studies of [177Lu]Lu-DOTMP and [177Lu]Lu-EDTMP radiopharmaceuticals indicated that [177Lu]Lu-DOTMP is quickly washed out from blood circulation and has lower retention in the non-target organs compared to EDTMP complexation [14]. This ligand has lower liver and kidney retention and good adhesion on bone tissue [14,17]. In addition, administration of [177Lu]Lu-DOTMP in high activities for animal models did not exhibit any clinical toxicity [20].

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. Some investigations concerned the dosimetric studies of bone-avid radiopharmaceuticals before preclinical trials in humans and animals with metastatic bone cancers. Radium-223-dichloride ([223Ra]$RaCl_2$) [30], Quadramet ([153Sm]Sm-EDTMP) [31,32], [166Ho]Ho-DOTMP [33], ([90Y]Y-EDTMP) [34], [186Re]Re-HEDP [35], [188Re]Re-HEDP [36], [141Ce]Ce-EDTMP [37] and [67Ga]Ga-phytate [38] are some bone-seeking radiopharmaceuticals that internal dosimetry studies of them were done.

However, the production, radionuclide, and radiochemical purity assessment and biodistribution studies of [177Lu]Lu-DOTMP radiopharmaceutical for some animals (dogs, rabbits, and rats) have been reported in some articles [9,14-21], but they did not evaluate the radiation absorbed dose and effective dose of this radiopharmaceutical for human neither directly (using nuclear medicine imaging) nor indirectly (using small animals models). In other words, there is no thorough preclinical and clinical work on the biokinetics and dosimetry studies of this radiopharmaceutical in humans. Although the biodistribution of radiopharmaceuticals in the human body must be considered with nuclear medicine imaging equipment as a basis for the absorbed dose assessments, in this research for the first time, it was tried to estimate the radiation absorbed dose from [177Lu]Lu-DOTMP radiopharmaceutical to humans based on previously published biodistribution data in Wistar type rats [14,17]. In addition, the maximum administrated activity of [177Lu]Lu-DOTMP radiopharmaceutical is suggested per one-kilogram body weight of an adult man, and the effective dose of this radiopharmaceutical is estimated.

Materials and Methods

Biodistribution studies of [177Lu]Lu-DOTMP in Wistar rats

Production and quality control of [177Lu]Lu-DOTMP radiopharmaceutical has been fully described by Chakraborty et al. [14,17]. This research uses biodistribution data in Wistar rats from the aforementioned articles for radiation dose estimates of a recently introduced radiopharmaceutical of [177Lu]Lu-DOTMP in man. Briefly, the radiolabeled DOTMP agent with carrier-added lutetium-177 radionuclide was produced through (n,γ) reaction by irradiation of natural Lu_2O_3 (2.6% 176Lu). The target was bombarded for 21 d at the thermal neutron flux of 6×10^{13} n cm^{-2} s. Biodistribution studies were carried out using normal Wistar rats. Each animal received about 0.1 mL (3-4 MBq of 177Lu) radioactive solution through its tail vein. The 30 min, 3 h, 1 d, 2 d, and 7 d time intervals after injection were considered for autopsy. Five rats were sacrificed at each time interval and organs were weighed and counted in a flat-type NaI(Tl) scintillation counter. The 208 keV (11%) gamma-ray line of 177Lu was selected for activity measurement in each tissue. Distribution of the radiopharmaceutical in different organs was stated as percentage of injected activity per organ, (% IA/organ).

[177Lu]Lu-DOTMP's biodistribution 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 [177Lu]Lu-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 [177Lu]Lu-DOTMP radiopharmaceutical [39]. Based on this method, the percent of injected activity (%IA) in human organs is calculated as follows:

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

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	17.3
Trabecular (cancellous) bone	1000	Brain	1.8
Reference	[40]	Reference	[41,42]

Table 2. Tissue weighting factors, W_T, in the 2007 recommendations of ICRP, publication 103 [45]

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

The weight of selected organs of the adult man and normal Wistar rats is given in Table 1 [40-42].

In addition, the activity of each organ after injection of A_0 Bq of [^{177}Lu]Lu-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 Medical Internal Radiation Dose (MIRD) Committee method of the Society of Nuclear Medicine [43] was considered for the radiation absorbed dose calculations. 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, $D(r_T)$ is the radiation absorbed dose to a target organ, r_T, from source organs, r_S. $\tilde{A}(r_S)$ stands for the accumulated activity in the source organ, r_S. The accumulated activity is calculated by the following equation:

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

The $S(r_T \leftarrow r_S)$ 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 were extracted from the OLINDA/EXM version 1.0 (Organ Level Internal Dose Assessment/Exponential Modeling) software [44]. About 12 and 22 tissues were considered as source and target organs, respectively.

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 168 h post-injection, the time-activity curve of each source organ was integrated up to 168 h (7 days), and the area under the curve was considered as the accumulated activity until 168 h. In the second step, one mono-exponential function was considered as the rest of the time-activity curve from 168 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 168 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. It should be noted that the effective half-lives of different organs were calculated as counting-based time-activity curves in this research. As mentioned above, rats' organ counting was carried out by a flat-type NaI(Tl) scintillation counter. Four last time intervals (3 h, 1 d, 2 d, and, 7 d, except 0.5 h) were used for fitting mono-exponential functions to the time-activity curves of most source organs after 168 h.

In addition, the effective dose was calculated according to the latest recommendations of the ICRP publication 103 [45], 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 [45].

Results

[177Lu]Lu-DOTMP's biodistribution in Wistar rats and humans

The biodistribution of [177Lu]Lu-DOTMP radiopharmaceutical in different organs of Wistar rats is given in Figure 1 according to Chakraborty et al. [14,17] articles. The uncertainties are given in terms of one standard deviation.

As shown in Figure 1, the [177Lu]Lu-DOTMP radiopharmaceutical has fast blood clearance after 0.5 h. It is preferentially localized in the osteoblastic lesions, and almost no significant uptake is observed in soft tissue or any other major non-target organs after 1 day. The %IA/organ of radiopharmaceutical is retained almost constant in bone tissue up to 7 d. kidneys, muscle, intestine, and liver tissues include some activities just after injection of radiopharmaceutical.

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. Human bone surface absorption was considered as the ratio of trabecular (cancellous) and cortical (compact) bone surfaces. 62% and 38% of the total skeletal surface consists of trabecular and cortical bones, respectively [46]. Figure 2 shows that about 40% of the injected radiopharmaceutical is stored on the surface of the trabecular and compact bones. This ligand has lower retention in the muscle, lung, kidneys, and small intestine tissues compared to bone tissue in the first-time intervals post-injection (see Figure 2). The large fraction of muscle mass in the human body (about 40% of total body weight is muscle) and the major excretion route of this radiopharmaceutical through kidneys are the main reasons for this activity accumulation. The %IA in the remaining source organs was less than 0.3%.

The time-activity curves for source organs of humans are given in Figure 3 a and b per injection of 1MBq of [177Lu]Lu-DOTMP radiopharmaceutical. As shown in Figure 3, most of the activity is rapidly deposited on cortical and trabecular bone surfaces (about 0.14 and 0.23 MBq at 0.5 h post-injection, respectively). Approximately, after 1 half-life of 177Lu radionuclide, there are insignificant activities in organs except for bone tissue and, to some extent, for kidneys.

About 40% of the injected activity is excreted via the urinary tract in the first hours after injection. Therefore, the dose absorbed from the bladder wall and the dose delivered by its contents to other organs should not be forgotten. Unfortunately, Chakraborty et al. [14,17] do not report the %IA of the urinary bladder wall and its content. To make a rough estimate, accumulated urinary excretion data of a similar radiopharmaceutical ([177Lu]Lu-EDTMP) for humans [25] was employed. In this paper [25], fractionated urine samples were collected in the first 48 hours after radiopharmaceutical injection for humans.

The frequency of urination and the activity of each urination should be known to accurately estimate the bladder wall absorbed dose. Conservatively, the time points of 4, 8, 24, and 48 hours were considered as the number of bladder voids, according to Ball et al. [25] article. Bladder activity is considered to be zero after each voiding. The activity-time curve for bladder contents per injection of 1 MBq [177Lu]Lu-DOTMP is also given in Figure 3b.

Radiation absorbed dose calculations

The accumulated activities in the source organs of the adult man per injection of 1 MBq of the [177Lu]Lu-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 [177Lu]Lu-DOTMP radiopharmaceutical is observed in trabecular and cortical bone surfaces. This radiopharmaceutical was approximately removed from this tissue with a radiological half-life (T_R=161.5 h). Due to the fast excretion of [177Lu]Lu-DOTMP through the urinary tract, the urinary bladder has the greatest accumulated activity after the bone tissue.

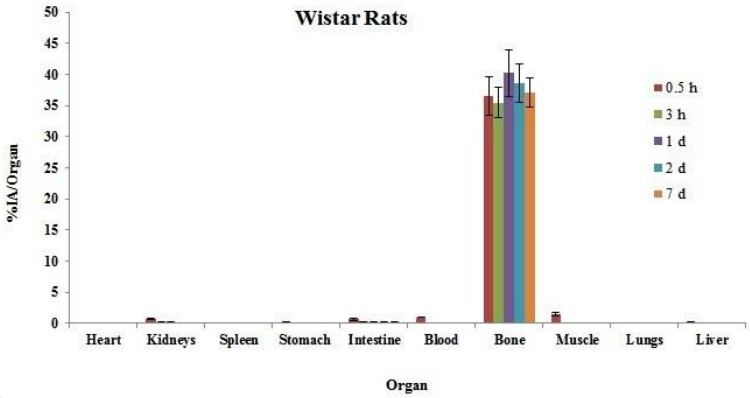

Figure 1. Percentage of the injected activity per organ (%IA/organ) of [177Lu]Lu-DOTMP in normal Wistar rats [14,17].

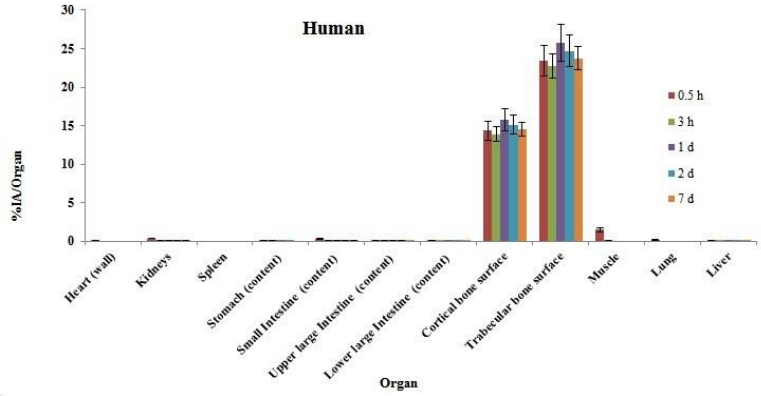

Figure 2. Percentage of the injected activity per organ (%IA/organ) of [177Lu]Lu-DOTMP in the adult man organs

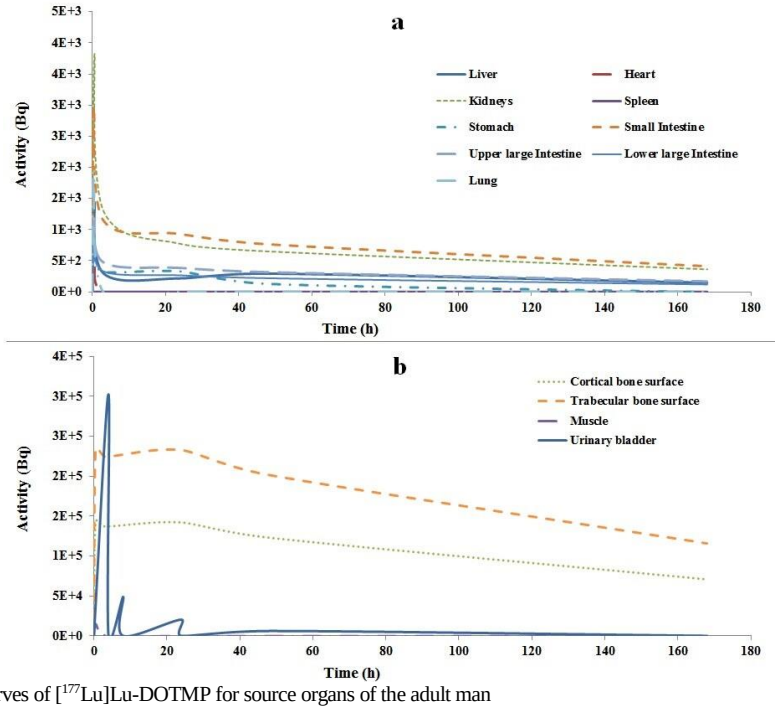

Figure 3. The time-activity curves of [177Lu]Lu-DOTMP for source organs of the adult man

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 [177Lu]Lu-DOTMP

Source organ	Accumulated activity	Effective half-life (h)	Source organ	Accumulated activity	Effective half-life (h)
Heart	2.2±0.2	0.3	Cortical bone surface	124744.1±9800.0	161.5
Kidneys	569.2±58.0	99.0	Trabecular bone surface	203529.8±15989.5	161.5
Stomach contents	78.2±11.8	18.7	Muscle	127.4±7.8	1.8
Small intestine contents	680.5±84.5	115.5	Lungs	10.6±0.3	0.2
Upper large intestine (ULI) contents	281.5±34.9	115.5	Liver	233.1±7.6	115.5
Lower large intestine (LLI) contents	193.1±24.0	115.5	Urinary bladder ontent	3378.7±270.3	---

Figure 4 shows a mono-exponential function fitted to the time-activity curve of the lower large intestine 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 0.006 h^{-1} (The effective half-life = 115.5 h) for LLI tissue with an R-squared value close to 1.

Evaluated radiation absorbed doses of an adult man per injection of 1 MBq [177Lu]Lu-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 observed for osteogenic cells and red bone

marrow about 0.89±0.07 and 5.12±0.40 mGy/MBq, respectively.

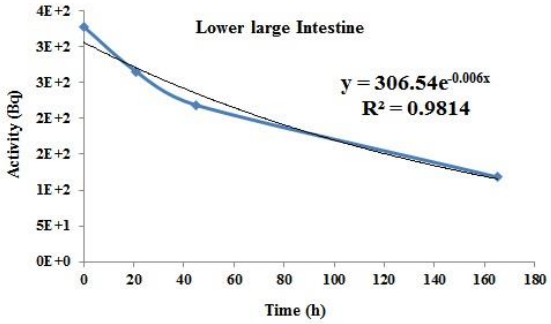

Figure 4. Fitting mono-exponential function to the time-activity curve of the lower large intestine tissue

The next organs with the highest radiation absorbed dose are the urinary bladder wall and kidneys with 0.20±0.02 mGy/MBq and 0.05±0.01 mGy/MBq, respectively. This fact indicates the rapid clearance of radiopharmaceutical from the circulation via the urinary tract. The effective dose of [177Lu]Lu-DOTMP radiopharmaceutical (0.19±0.02 mSv/MBq) was obtained lower than [166Ho]Ho-EDTMP (0.29 mSv/MBq) and 153Sm-EDTMP (0.21 mSv/MBq) radiopharmaceuticals (see Table 4) [47].

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 [48]. In addition, the maximum activity to be administered to patients in terms of MBq/kg of body weight is given in Table 5. 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 [177Lu]Lu-DOTMP radiopharmaceutical should not exceed 32.2 MBq/kg (0.87 mCi/kg) of body weight. This administrated activity will result in about an 11.6 Gy bone surface absorbed dose for a 70 kg adult man. As shown in Table 5, except for [90Y]Y-EDTMP radiopharmaceutical, the lutetium-177 radiopharmaceuticals ([177Lu]Lu-EDTMP and [177Lu]Lu-DOTMP) deliver more radiation absorbed doses to bone surfaces compared with other studied radiopharmaceuticals. However, it should be noted that [177Lu]Lu-EDTMP and [177Lu]Lu-DOTMP radiopharmaceuticals deliver a higher dose to the red bone marrow too (excluding [166Ho]Ho-EDTMP and [90Y]Y-EDTMP).

Table 4. The radiation absorbed doses (mGy/MBq) of the adult man's target organs per injection of 1 MBq of [177Lu]Lu-DOTMP radiopharmaceutical

Target organs	Absorbed dose	Target organs	Absorbed dose
Adrenal	0.010±0.001	Muscle	0.007±0.001
Brain	0.011±0.001	Pancreas	0.006±0.000
Breasts	0.003±0.000	Red marrow	0.886±0.070
Gallbladder wall	0.004±0.000	Osteogenic cells	5.119±0.402
Lower large intestine (LLI) wall	0.023±0.003	Skin	0.005±0.000
Small intestine	0.025±0.003	Spleen	0.005±0.000
Stomach wall	0.007±0.001	Testes	0.004±0.000
Upper large intestine (ULI) wall	0.020±0.002	Thymus	0.004±0.000
Heart wall	0.005±0.000	Thyroid	0.007±0.001
Kidneys	0.051±0.005	Urinary bladder wall	0.198±0.016
Liver	0.008±0.000	Total body	0.115±0.009
Lungs	0.006±0.000	Effective dose (mSv/MBq)	0.186±0.015

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

Tissue	[90Y]Y-EDTMP	[153Sm]Sm-EDTMP	[166Ho]Ho-DOTMP	[166Ho]Ho-EDTMP	[186Re]Re-HEDP	[188Re]Re-HEDP	[177Lu]Lu-EDTMP	[177Lu]Lu-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
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
Max. administered activity (MBq/kg)	15.7	41.4	55.7	20.1	31.4	47.1	27.1	32.2
Bone surface absorbed dose (mGy/MBq)	18	4.3	0.9	3.1	3.1	3.8	6.2	5.1
Bone marrow absorbed dose (mGy/MBq)	1.8	0.7	0.5	1.4	0.9	0.6	1.1	0.9
Reference	[34]	[32]	[33]	[48]	[35]	[36]	[3]	This work

Discussion

[^{177}Lu]Lu-DOTMP radiopharmaceutical showed massive accumulation in the cortical and trabecular bone surfaces, which remained constant until the next 7 days. The complex was rapidly cleared from the blood and no significant uptake was observed in other vital organs.

Radiolabeled phosphonates such as [^{177}Lu]Lu-EDTMP and [^{177}Lu]Lu-DOTMP, tend to localize uniformly to cortical and trabecular bone surfaces [48,49]. Most of the activity distributed over the bone tissue was deposited on the surface of the trabecular bone due to the larger surface area of the trabecular bone versus the cortical bone (10.5 m^2 vs. 6.5 m^2) [46]. Due to the strong adhesion of DOTMP to bone tissue, biological removal of this radiopharmaceutical from bone tissue can be neglected.

According to various phosphonate ligands labeled with beta-emitting radionuclides [3,31-38,47-50], skeletal tissue receives a more radiation absorbed dose from lutetium-177 for bone pain palliation purposes. The intermediate-energy beta particles of ^{177}Lu compared to high-energy beta particles of ^{166}Ho and ^{153}Sm radionuclides are responsible for a lower effective dose of [^{177}Lu]Lu-DOTMP radiopharmaceutical. It should be noted that the clinical studies with the DOTMP agent led to the successful injection of [^{177}Lu]Lu-DOTMP radiopharmaceutical up to 3.7 GBq (100 mCi) [51]. The ^{177}Lu-DOTMP has slightly faster blood clearance and less retention in the liver and kidneys compared to ^{177}Lu-EDTMP radiopharmaceutical [14,17].

Although extrapolation between nonhuman primates (e.g., beagles, baboons, rabbits, mice, and rats) and humans may result in overestimation or underestimation of absorbed dose, several articles previously published in the literature have justified the usefulness of this method for preclinical and initial absorbed dose estimations of newly developed radiopharmaceutical [47,50]. However, imaging studies are the main method for assessing the absorbed dose of radiopharmaceuticals in nuclear medicine.

Conclusion

The radiation absorbed dose, effective dose, effective half-lives, and accumulated activities for [^{177}Lu]Lu-DOTMP radiopharmaceutical in adult men were evaluated based on biodistribution data in Wistar rats. The results indicate that per unit of injected activity of the [^{177}Lu]Lu-DOTMP radiopharmaceutical, osteogenic cells will receive approximately 6 times more radiation dose than red bone marrow. Although lutetium-177 radiopharmaceuticals' bone surface absorbed doses are not comparable to [^{90}Y]Y-EDTMP, their delivered doses to bone surface are higher than other studied radiopharmaceuticals. Our study provides a theoretical basis for subsequent clinical dosimetry studies of [^{177}Lu]Lu-DOTMP in numerous patients with developed bone metastasis to estimate the complete effectiveness and safety of this recently introduced radiopharmaceutical as a bone pain palliation agent.

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