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Pharmacokinetic studies and human absorbed dose estimation of ^{68}Ga-(4 {[(bis (phosphonomethyl)) carbamoyl] methyl}-7,10-bis(carboxymethy l) -1,4,7,10 -tetraazacyclododec-1-yl) acetic acid

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► ***Original article***

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ABSTRACT

Background: In this study, human absorbed dose of a newly introduced bone imaging agent, 68Ga-(4-{[(bis(phosphonomethyl))carbamoyl]methyl}-7,10-bis (carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl) acetic acid (68Ga-BPAMD), was estimated based on the rats data. ***Materials and Methods***: ^{68}Ga was obtained from the ^{68}Ge/^{68}Ga generator and it's radionuclidic and radiochemical purities were investigated. ^{68}Ga-BPAMD complex was prepared at optimal conditions and the radiochemical purity was studied using instant thin layer chromatography (ITLC) method. The final preparation was injected to the normal rats and the biodistribution of the complex was followed up to 120 min post injection. The accumulated activity for animal organs was calculated. Finally, the human absorbed dose of the complexes was estimated by RADAR method. ***Results:*** ^{68}Ga-BPAMD complex was prepared in high radiochemical purity (>99%, ITLC) at optimal conditions. The biodistribution of the complex demonstrated that the main remained radioactivity would considerably accumulate into the bones. The results showed the highest amounts of absorbed dose on the bone surface (0.253 mGy/MBq) and in the bone marrow (0.250 mGy/MBq), while the other organs would receive an insignificant absorbed dose after injection of the ^{68}Ga-BPAMD complex. ***Conclusion:*** The comparison of dosimetric results for ^{68}Ga-BPAMD with other complexes shows this complex is a safer agent for bone scanning. This property as well as other characteristics such as the high resolution images of the positron emission tomography (PET) scanning and the availability of ^{68}Ga in the form of ^{68}Ge/^{68}Ga generator, make this complex as a suitable agent for PET bone imaging.

Keywords: *Absorbed dose, Bone metastases, BPAMD, Ga-68, Positron emission tomography.*

INTRODUCTION

While, the bones are the most common sites of metastatic diseases [1] and bone metastases can result in severe effects such as pain, spinal cord compression, hypercalcemia and pathologic fracture [2], early detection of skeletal metastasis is critical for accurate staging and optimal treatment [3].The radionuclide bone scan can be considered as an excellent modality for the detection of metastasis in patients suffering from primary malignancies [4].

Nowadays, a large number of bone-seeking radiopharmaceuticals using bisphosphonates have been introduced. The large majority of radionuclide imaging studies performed worldwide are currently based on ^{99}Mo/^{99m}Tc generator [6].^{99m}Tc labelled methylene

diphosphonate (^{99m}Tc-MDP) is the most frequently used radiotracer for diagnostic purposes using SPECT [5]. Due to the higher spatial resolution of PET compared with SPECT, ^{18}F-FDG is now being used as a useful tool for imaging. In the recent years, some new complexes of ^{18}F including ^{18}F–NaF has been developed showing its superiority against ^{99m}Tc-MDP and ^{18}F-FDG PET/CT in the investigation of bone metastasis [6].

The interesting physical properties and availability of gallium-68 as a ^{68}Ge/^{68}Ga generator make it an interesting nuclide for developing new PET tracers [7].^{68}Ga-labelled oxine has been used in RBC labelling since 1977 [8].While different ^{68}Ga- based radiopharmaceuticals including somatostatin analogues have been employed in clinical trials [9], some radiolabelled complexes of this radionuclide have been developed and are being under evaluation for the diagnosis of bone malignancies [10].

Lately, a new macrocyclic diphosphonate, (4- { [(bis (phosphonomethyl)) carbamoyl] methyl } - 7, 10 -bis (carboxymethyl) - 1,4,7,10-tetraazacyclododec -1-yl) acetic acid (BPAMD), have been presented overcoming some of the restrictions of EDTMP. In the recent research studies, BPAMD labeled with ^{68}Ga showed high in vitro stability and high binding to hydroxyapatite. Besides, PET imaging of bone metastases bearing rats after ^{68}Ga-BPAMD injection revealed high accumulation in the bone metastases [11].

In the first human study in a patient with extensive bone metastases of prostate cancer, intense accumulation of ^{68}Ga-BPAMD in multiple osteoblastic lesions was observed [12]. According to the results of this research, it is suggested as an ideal PET/CT tracer to plan and monitor bisphosphonate therapy in several bone disorders and also to monitor radionuclide therapy for palliation of bone pain.

Estimation of the absorbed dose in target and non-target organs is one of the first steps in developing new radiopharmaceuticals which can evaluate the risks associated with the administration of radiopharmaceuticals and thus the maximum amount of activity that should be undertaken [13]. Any extra radiation dose can damage the healthy tissue and result in serious complications. It is generally recognized that even a 10% reduction in patient dose is a worthwhile objective [14].Nevertheless, the absorbed dose of human organs after injection of ^{68}Ga-BPAMD has not been reported until now.

In this study, in view of the importance of absorbed and effective dose estimates in nuclear medicine and with regard to the desirable characteristics of ^{68}Ga-BPAMD as a bone-seeking agent, the absorbed dose of human organs after injection of this radiolabeled compound was estimated based on biositribution data in male Syrian ratsand according to the radiation absorbed dose assessment resource (RADAR) method.For this purpose, the accumulated activity of human organs was determined by extrapolating the accumulated activity of animal organs using the proposed method of Sparks *et al.* [15].

MATERIALS AND METHODS

The ^{68}Ge/^{68}Ga generator with the nominal activity of 30 mCi was obtained from Pars Isotope Co. (Tehran, Iran). BPAMD was provided from ABX (Radeberg, Germany). All other chemical reagents were purchased from Merck (Darmstadt, Germany). Whatman No. 2 paper was obtained from Whatman (Buckinghamshire, U.K.). A high purity germanium (HPGe) detector coupled with a Canberra™ (model GC1020-7500SL) multichannel analyzer was used for the measurement of the activity and assessment of gamma impurities. Activity calculations were accomplished based on the 511 keV photon peak related to ^{68}Ga. Radio-chromatography was performed by using a bioscan AR-2000 radio TLC scanner instrument (Bioscan, Washington, DC, USA).For chemical purity determination, an ICP-OES spectrometer (Varian Co., model Turbo-AX-150-Liberty) was employed. Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines [16]. All rats weighing 180-220 g (n=4) were kept at routine day/night light program and under common rodent diet pellets. All values were

expressed as mean ± standard deviation (Mean ± SD) and the data were compared using student *t-test*. Statistical significance was defined as P<0.05.

Preparation and quality control of $^{68}GaCl_3$ solution

In order to prepare $^{68}GaCl_3$ solution, the generator was eluted with 0.6 M HCl. In order to optimize the minimum required volume with the maximum radioactive concentration, the generator was eluted with 0.5 mL hydrochloric acid alternatively and each fraction was gathered in a separate vial. Whereas only 0.5% of the total activity was observed in the first 0.5 mL fraction, 90% of the whole 68Ga eluted activity was achieved in the four subsequent fractions. Therefore, the first fraction of the generator eluted by 0.5 mL of HCl was disregarded and the four next fractions (2.0 mL) were considered for radiolabeling purposes. The radionuclidic and radiochemical purities were investigated in accordance with the reported procedure by gamma spectrometry and RTLC methods, respectively [17].

Preparation and quality control of ^{68}Ga-BPAMD

30 µL of BPAMD solution (1 mg/mL) was added to a borosilicate vial containing a certain volume of $^{68}GaCl_3$ (about 555 MBq). The vial was putted in a hot water bath (with 90 °C) for 15 min while its pH was adjusted equal to 5. Finally, the radiolabeled compound was passed over the strong cation exchanger (Strata-X-C 60 mg) preconditioned with 1 mL 4 M HCl and 1 mL water, respectively. The radiochemical purity of the final compound was checked by ITLC method using NH_4OH: MeOH: H2O (2:20:40) mixture and Whatman No.2 paper.

Biodistribution assessment of ^{68}Ga-BPAMD in male Syrian rats

100 µL of the final radiolabeled compound (with approximately 5.55MBq radioactivity) was injected intravenously into the male Syrian rats through their tail veins. The rats were sacrificed at the selected intervals (15, 30, 60 and 120min) after injection (n=4).The tissues were rinsed with normal saline, the weight was determined with a calibrated balance and the activity of each organ was determined with a p-type coaxial HPGe detector using equation 1 [18].

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

where, ε is the efficiency at photopeak energy, γ is the emission probability of the gamma 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 equation 2:

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

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_s is the live time of the background spectrum collection in seconds. Eventually, the non-decay corrected percentage of the injected dose per gram (%ID/g) for different organs was calculated.

Statistical analysis

Four rats were sacrificed for each interval. All values were expressed as mean ±standard deviation and the data were compared using Student's *t-test*. The statistical significance was defined as p<0.05.

Calculation of accumulated activity for each animal organ

The non-decay corrected percentage-injected activity versus time was plotted for each animal organ according to equation 3.

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

Where; A(t) is the activity of each organ at time t.

The curves were extrapolated to infinity by

fitting the tail of each curve to a mono exponential curve with the exponential coefficient equal to the physical decay constant of each radionuclide. Whereas, the activity of blood at t=0 was considered as the total amount of the injected activity, the activity of all other organs was assumed to be zero at that time.

Estimation of accumulated activity for human organs

The cumulated activity for animal organs was extrapolated to the cumulated activity for human organs by the proposed method of Sparks *et al.* [19] (equation 4). In order to extrapolate this cumulated activity to human, the standard mean weights for each human organ were used [20].

$$\tilde{A}_{Human\,organ} = \tilde{A}_{Animal\,organ} \times \frac{Organ\,mass_{human}/Body\,mass_{human}}{Organ\,mass_{animal}/Body\,mass_{animal}} \quad (4)$$

Equivalent absorbed dose calculation

The absorbed dose in human organs was calculated by RADAR formalism based on biodistribution data in Syrian rats [21] (equation 5):

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

Where $\tilde{A}$ is the accumulated activity for each human organ, and DF is defined as equation 6:

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

In the this equation, 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 ($\frac{mGy.kg}{MBq.s.MeV}$). According to Equ. 5, the calculated cumulated activity for each source organ was multiplied by the dose factors (DFs) for the related organ. The total absorbed dose for each target organ was computed by the summation of the absorbed dose delivered from each source organ. For this research, DFs have been derived from the data reported in OLINDA/EXM software [22].

Effective absorbed dose calculation

The equation 7 was used to calculate the effective absorbed dose of organs.

$$E = \sum_T W_T H_T \quad (7)$$

where H_T is the equivalent absorbed dose for each organ and W_T is the tissue-weighting factor [23] and obtained from the reported value in ICRP 103 [24].

RESULTS

Quality control of $^{68}GaCl_3$

A p-type coaxial HPGe detector was applied to evaluate any gamma-emitter impurities in $^{68}GaCl_3$ solution. Whereas, the samples were counted for 1,000 s after 48 h of the generator elution, the spectrum showed the presence of 511 and 1077 keV, all originating from ^{68}Ga.

Radiochemical purity of $^{68}GaCl_3$ sample was checked using ITLC method and by means of two solvent systems (10 mM DTPA, 10 % ammonium acetate: methanol mixture (1:1)) showing the purity of more than 99.9%.

Preparation and quality control of ^{68}Ga-BPAMD

^{68}Ga-BPAMD was prepared with specific activity of about 9.5 GBq/µmol. Radiochemical purity of the radiolabeled complex was assessed by ITLC method using NH_4OH:MeOH:H_2O (2:20:40) as the mobile phase. The free cation remains at the origin while the radiolabelled compound migrates to higher R_f (0.8) (figure 1). As shown in the Figure 1, the radiochemical purity of the complex was more than 99 %.

Biodistribution of radiolabeled complexes in Syrian mice

The percentage of the injected dose per gram in rat organs up to 120 min after injection of the radiolabeled complex was determined. The non-decay corrected clearance curves from the main organ sources of the rats for ^{68}Ga-BPAMD are shown in figure 2. As expected major portion

of the injected radioactivity remaining in the body is transferred from the blood circulation into the bone.

Equivalent absorbed dose calculation

Absorbed dose of different human organs after injection of ^{68}Ga-BPAMD was calculated using RADAR formalism based on biodistribution data in the Syrian rats (table 1). As expected, the highest amounts of the absorbed dose after ^{68}Ga-BPAMD was observed on the bone surface (0.253mGy/MBq) and in the bone marrow (0.250 mGy/MBq). For better comparison, the estimated effective absorbed dose of ^{111}In-BPAMD [25] has been presented in the table too.

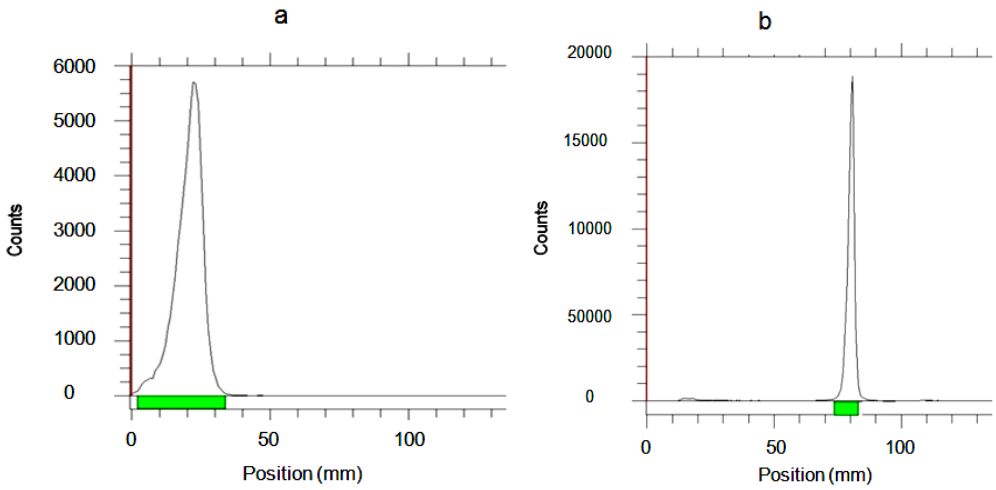

Figure 1. ITLC chromatogram of 68Ga-BPAMD **(a)** and 68GaCl3 **(b)** in NH4OH:MeOH:H2O (2:20:40) using Whatman No. 2 as a stationary phase.

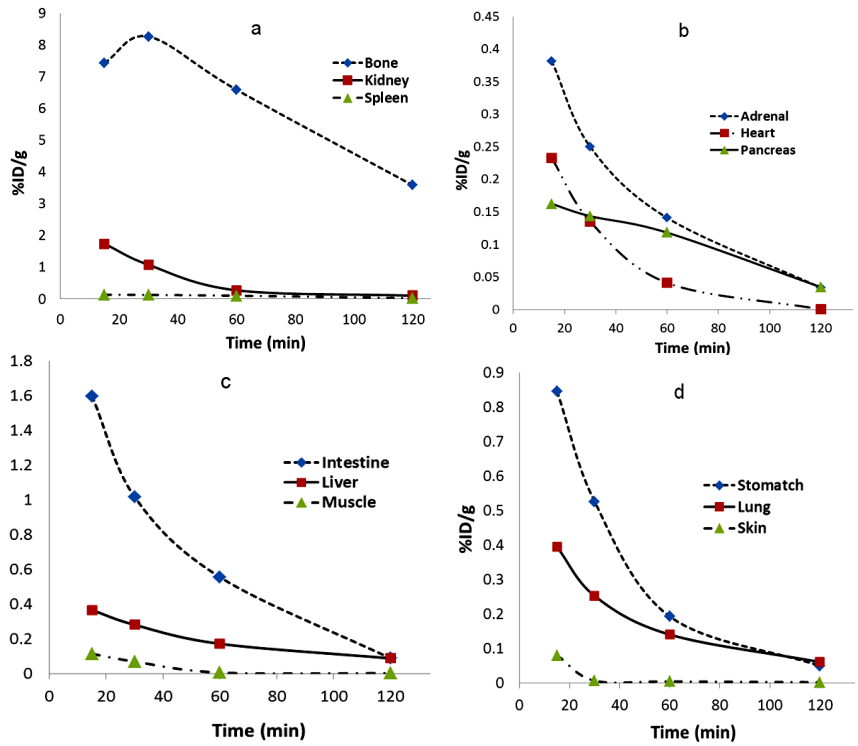

Figure 2. Non-decay corrected clearance curves for bone, kidney, spleen **(a)**; adrenal, heart, pancreas **(b)**; intestine, liver, muscle **(c)**; stomach, lung and skin **(d)** of Syrian rats after intravenously injection of 68Ga-BPAMD.

Table 1. Equivalent and effective absorbed dose delivered into human organs after injection of 68Ga-BPAMD; Comparison with 111In-BPAMD.

Target Organs	^{68}Ga-BPAMD			^{111}In-BPAMD
	Equivalent absorbed dose in humans (mGy/MBq)	Wt[a]	Effective absorbed dose in humans (mSv/MBq)	Effective absorbed dose in humans (mSv/MBq)
Adrenals	0.011	0.12	0.0013	0.011
Brain	0.009	0.01	0.0000	0.001
GB Wall	0.004	0.12	0.0005	0.050
LLI Wall	0.054	0.12	0.0065	0.009
Small Int	0.005	0.12	0.0006	0.006
Stomach Wall	0.005	0.12	0.0006	0.005
ULI Wall	0.004	0.12	0.0005	0.005
Heart Wall	0.006	0.12	0.0007	0.007
Kidneys	0.014	0.12	0.0017	0.008
Liver	0.009	0.04	0.0004	0.002
Lungs	0.009	0.12	0.0011	0.003
Muscle	0.006	0.12	0.0007	0.008
Pancreas	0.008	0.12	0.0010	0.007
Red Marrow	0.250	0.12	0.0300	0.040
Bone Surf	0.253	0.01	0.0025	0.009
Spleen	0.006	0.12	0.0007	0.006
Testes	0.003	0.12	0.0004	0.004
Thymus	0.004	0.12	0.0005	0.005
Thyroid	0.006	0.04	0.0002	0.003
UB Wall	0.003	0.04	0.0001	0.002
Total Body	0.028		0.050	0.205

DISCUSSION

Nowadays, ^{99m}Tc-MDP approved by the US Food and Drug Administration (FDA) is used as the standard clinically agent for SPECT bone imaging. However, due to the some limitations such as slow clearance from the soft tissues reported using this radiolabelled compound which can result in the considerable absorbed dose to the non-target organs [26], researchers are going to develop new agents with larger ratio of bone to soft tissue uptake.

With the introduction of BPAMD as a novel DOTA-based bisphosphonate in the recent years, labeling of this ligand with different therapeutic and diagnostic radionuclides has been reported [27-28-29]. In these days of ^{99m}Tc shortage, recent studies are focusing on the other diagnostic radionuclides including ^{18}F, ^{68}Ga, ^{67}Ga and ^{111}In.Among them, ^{68}Ga with the interesting physical properties and availability as a ^{68}Ge/^{68}Ga generator which provide images with higher spatial resolution compared to the gamma-emitting radionuclides, is recognized as an ideal choice and many researches has been carried out on the radiolabelled compounds of this radionuclide to date.

Production and quality control of ^{68}Ga-BPAMD and ^{111}In-BPAMD has been reported indicating high bone to soft tissue uptake ratio [30]. The amounts of absorbed dose of different human organs after ^{111}In-BPAMD injection has been presented previously based on biodistribution data in male Syrian rats [31]. Although, estimation of the absorbed dose from rats to human may make some underestimation or overestimation, but it is a common first step consistent with the ICRP 62 recommendations [32].

In this research, with respect to the great

results observed in the first human study after ^{68}Ga-BPAMD injection, the absorbed dose of different human organs was computed which can be used for determining the maximum permissible administered activity. The equivalent absorbed dose value for bone surface in the case of ^{68}Ga-BPAMD is three times lesser than this value for ^{111}In-BPAMD usage. Also, the absorbed dose of total body is more than 4.5 times greater in the case of ^{111}In-BPAMD usage. For the other organs, the comparison shows the much lesser absorbed dose values for ^{68}Ga-BPAMD.

CONCLUSION

In this study, ^{68}Ga-BPAMD was prepared with radiochemical purity of >99% as a suitable PET bone imaging agent in 15 min. The absorbed dose estimations of human organs were done according to the RADAR and Spark *et al.* methods. The results showed the highest amounts of absorbed dose on the bone surface and in the bone marrow with the amounts of 0.253 and 0.250 mGy/MBq, respectively, while the other organs would receive an insignificant absorbed dose after injection of the complex. Therefore, the use of ^{68}G-BPAMD in PET bone scanning, in addition to the high resolution images can result in insignificant absorbed dose in most organs as well as total body. These characteristics make this complex as a suitable and safe agent for PET bone imaging.

***Conflicts of interest*:** *Declared none.*

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