TECHNICAL NOTE

Critical Organ Dose Estimation from Tc-99m-MIBI in Nuclear Medicine Cardiology Based on Distribution Data in Rats

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Abstract

Purpose: Calculating the organs' radiation dosage in cardiac nuclear medicine procedures is essential in order to identify critical organs, radiation risk assessment and optimization dose value in the injection of radiopharmaceutical drugs. In this study, the biological distribution of 99mTc-2-Methoxyisobutylisonitrile) 99mTc-MIBI as the most common radiopharmaceutical in a cardiac study in human organs based on animal samples was investigated.

Materials and Methods: After ^{99m}Tc-MIBI preparation, radiopharmaceutical was injected into 15 rats. After sacrificing rats, the uptake of radiopharmaceuticals in critical organs at 15, 30, and 45 minutes was measured using an High Purity Germanium (HPGE) detector and the percentage of injected dose per gram of organs was calculated. The cumulative activity was calculated from the radiopharmaceutical transformation diagram with time. The absorption of a radioactive complex in human organs based on animal data was calculated by applying a correction factor. The organs dose was calculated using S factor and the effective dose was calculated using tissue weighting factors.

Results: The mean effective dose per unit of activity was 0.0062 mSv/MBq. The mean effective dose of 27.5 mCi radiopharmaceutical injection was 6.3 mSv. In this study, the absorbed dose in blood, heart, lung, thyroid, liver, spleen, stomach wall, muscle, and bone was calculated as 0.28, 2.92, 1.85, 24.82, 11.13, 7.03, 20.95, 1.11, 4.97, and 22.22 mGy, respectively.

Conclusion: The effective dose of human organs based on the animal model in the study of cardiac nuclear medicine was evaluated by injection of ^{99m}Tc-MIBI radiopharmaceutical. The kidneys, salivary glands, thyroid, and spleen were the most critical organs that should be considered in dose optimization studies. The effective dose limit was 28% lower than the values reported in international references.

Keywords: Absorption Dose; Biodistribution; Internal Dosimetry; Nuclear Medicine; 99Tc-Methoxyisobutylisonitrile.

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Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Absorbed dose calculations of human organs provide a scientific basis for calculating the biological effects and radiation risk resulting from the injection of radiopharmaceutical in nuclear medicine studies. In the treatment of cancer using ionizing radiation, dosimetry is very necessary to design the treatment of the target area, analyze the dose-response curve, evaluation and prediction the effectiveness of treatment and complete the patient's radiation dose documents [1]. Today, new imaging methods and the use of new radiopharmaceuticals in the field of nuclear medicine are expanding, so accurate dosimetry process and introduction of patient dose calculation methods to optimize techniques and radiation risk calculation is of great importance [2]. In dosimetric studies in nuclear medicine in vivo, exposure of human samples is faced with obstacles of the ethics code, so in order to optimize technical methods in nuclear medicine studies and calculate the organs dose, the use of alternative samples is necessary [3]. The information obtained from the distribution of new radiopharmaceuticals in the living environment in animal studies makes it possible to evaluate the patients' radiation dose [1]. Much available data on organ doses after radiopharmaceutical injection in nuclear medicine relates to Monte Carlo calculations on mathematical phantoms or is based on direct measurements and the use of conversion coefficients [4-6]. Numerous codes for internal dosimetry have been developed and introduced in nuclear medicine, which differ in dosimetry technique, phantom type, and other cases. The variety and multiplicity of dose values of organs is due to the use of multiple codes by researchers. The most popular codes for dose calculation are MABDOSE designed by the University of Colorado [7], OLINDA / EXM which is an upgraded version of MIRDose [8, 9] and RADAR which uses anatomical models based on the NURBS hybrid phantom [10]. MIRDose is one of the most important organ dose calculation software in nuclear medicine that has been used by many researchers. This software is introduced by Radiation Internal Dose Information Center. This software contains S value tables of common radionuclides. In order to calculate the dose of organs in this software, the biokinetic information of radiopharmaceuticals and the duration of the presence of the drug in each source organ (residence time) should be introduced as input information and, mathematical phantoms of the human body have been used [5]. One of the problems of this software is that the user has to extract the biokinetics of radiopharmaceuticals from animal or human data in order to calculate the organs dose [11]. In this study, residence time was measured directly based on radiopharmaceutical biodistribution curves.

The role of the Technetium-99m (^{99m}Tc) in nuclear medicine is well known. This radioactive element with gamma-ray radiation with 140 keV energy and a half-life of 6 hours is commonly used in nuclear medicine procedures. So, it is necessary to investigate the possible risks of injection of this radionuclide and measure the absorbed dose in the patient's organs to evaluate the benefits and risks of use [12]. Single-Photon Emission Computed Tomography (SPECT) imaging system in nuclear medicine has played an important role in diagnosing coronary disease, myocardial infarction, prognosis, risk assessment, and evaluation of ventricular function. The radiopharmaceutical biodistribution in organs depends on the type of combination of the drug bound with the radioactive substance [13]. It is impossible to estimate the radiation dose of patients' internal organs in vivo situation and to do so, computer simulation methods or generalization of radiopharmaceutical behavior in organs of animal samples to human samples are performed. In this study, the biodistribution of ^{99m}Tc-MIBI as the most common radiopharmaceutical in the cardiac study was investigated in human organs based on animal samples and the dose of organs resulting from the accumulation of radioactive material was assessed.

2. Materials and Methods

2.1. Preparation of ^{99m}Tc Radioactive Material and Bonding it with MIBI

Technetium-99 (^{99}Tc) was obtained from the transformation of Molybdenum-99 (Mo-99) in a column of aluminum oxide in a generator produced by the Atomic Energy Organization of Iran. The ^{99}Tc milked from the generator was diluted at room temperature using normal sterile saline 0.9% by weight. The milked solution was used as a sodium pertechnetate solution for the next steps. Preparation and labeling of MIBI (methoxy isobutyl isonitrile) with ^{99m}Tc according to the kit preparation method was performed in TGS No. 466 of the International Atomic Energy Agency [14].

2.2. Investigation of ^{99m}Tc-MIBI Biological Distribution in Rat Body

In all stages of this study, animal interventions were performed in accordance with the guidelines of the British Biological Institute for the use of live animals in scientific research [15]. To determine the distribution of ^{99m}Tc-MIBI in the body of rat, 100 microliters of the prepared solution with an activity of 7 to 7.4 MBq were injected through the tail vein into 15 rats. All rats were anesthetized with ethyl ether before injection. At each stage, 5 rats were killed using CO2 gas chamber at 15, 30, and 45 minutes after injection of radiopharmaceutical. Critical organs of the rats, including blood, heart, liver, right kidney, left kidney, muscle, a sample of trabecular bone, intestine, stomach, tail, spleen, and adrenal gland were isolated. The organs were washed with normal saline and then dried. The samples were weighed and counted 3 times using HPGe detector. In order to reduce the statistical uncertainty, 10,000 counts were performed each time until the standard deviation reached less than 1%. Then, the percentage of injected dose per gram of organs (Injected dose per gram -% ID / g) of rat was measured. For this purpose, the area under the counting curve against time, drawn by the HPGe detector at 140.51 keV (technetium transformation), was calculated [16]. Two samples of organs of control rats that were not injected with radiopharmaceutical were counted as well as the samples injected to remove the background radiation. Radioactive material activity in injected complex was measured in pre-injection and post-injection syringes using well-type ionization chambers of Capintec CRC-15R made in USA [17]. The effect of background radiation was removed for all samples. The percentage of the dose injected per gram of organ is equal to the percentage of activity injected per gram of organ (% IA/g = % ID /g) [18]. The activity concentration of ^{99m}Tc-MIBI at time t, was calculated as the percentage of injected activity per gram of tissue displayed with Ctissue [19] (Equation 1).

$$C_{tissue}(t) = \frac{A_{tissue}(t)/\,M_{tissue}}{A_{total}} \times 100 \qquad (1)$$

Where A_{tissue} (t) is the activity of technetium at time t, M_{tissue} is the mass of each organ, and A_{total} is the total activity of ^{99m}Tc-MIBI injected into rat.

2.3. Calculating the Dose of Patients' Organs

To calculate the organ dose, first, the total transformations of ^{99m}Tc-MIBI as cumulative activity ($\tilde{A}_h$) were obtained from Equation 2.

$$\widetilde{A_h} = \int_t^{\infty} \widetilde{A_h}\,(t)dt \qquad (2)$$

Where A_h is the activity (% IA/g) at time t. The Cumulative activity was calculated by measuring the area under the exponentially fitted curve with % IA/g point data over time. The regression coefficient of the fitted curve was considered above 0.9. Excel software was used to obtain the fitted Equations. The absorption of radiopharmaceutical complex into human organs from an animal sample as correction factor was extracted using Equation 3 by the method proposed by Sparks and Aydogan [20]:

$$\tilde{A}_{human\ organ} = \tilde{A}_{animal\ organ} \times \left[\frac{Organ_{masshuman}/Body_{masshuman}}{Organ_{massanimal}/Body_{massanimal}}\right] \qquad (3)$$

This correction factor was calculated based on data extracted from ICRP and Medical Internal Radiation Dose (MIRD), which is provided for 6 age groups of both sexes [21]. Equation 4 was used to calculate the absorbed dose in the organs [22].

$$\tilde{D}(r_k) = \sum_h \widetilde{A_h}\, S(r_k \leftarrow r_h) \qquad (4)$$

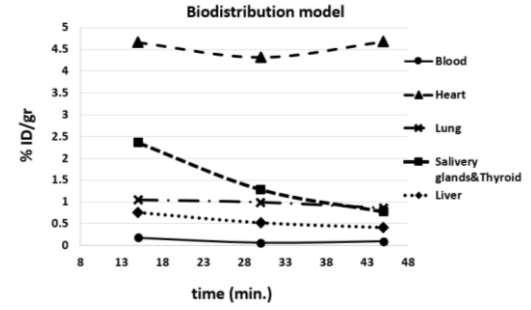
Where, D (r_k) is the absorbed dose in the target organ, A_h, is the cumulative activity in the source organ and the value of S ($r_k \leftarrow r_h$) is the average absorbed dose in the target organ (r_k) from the unit of activity accumulated in the source organ (r_h) [6, 23]. Equation 5 was used to calculate the effective dose.

$$E = \sum_T W_T\, H_T \qquad (5)$$

Where H_T is the equivalent dose in each tissue or organ (in terms of beam quality factor) and W_T is the tissue weight factor [2].

3. Results

In this study, the biodistribution of ^{99m}Tc-MIBI complex in the body of a rat and the time course of accumulation of this substance in critical organs of rats were investigated. Figures 1a and 1b show the biodistribution model measured in all critical organs of the rats.



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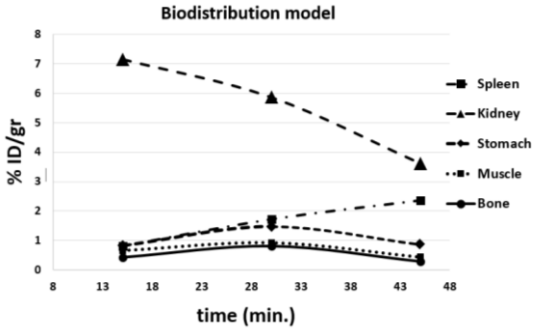

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Figure 1. Biodistribution of ^{99}Tc-MIBI radiopharmaceuticals in critical organs of rat. (a) for blood, heart, lung, thyroid, liver, and diagram (b) for spleen, kidney, stomach, muscle, and bone

Table 1. Fitted equation of biodistribution curves in rats organs to calculate cumulative activity

Rats critical organs	Bio distribution equations
blood	$3E\text{-}06x^2 - 0.0002x + 0.0044$
Heart	$2E\text{-}05x^2 - 0.0009x + 0.0571$
Lung	$-2E\text{-}06x^2 + 4E\text{-}05x + 0.0102$
Salivary glands &Thyroid	$1E\text{-}05x^2 - 0.0013x + 0.0401$
Liver	$3E\text{-}06x^2 - 0.0003x + 0.0114$
Spleen	$-6E\text{-}06x^2 + 0.0009x - 0.0039$
Kidney	$-2E\text{-}05x^2 + 9E\text{-}05x + 0.0751$
Stomach	$-3E\text{-}05x^2 + 0.0017x - 0.0106$
Muscle	$-2E\text{-}05x^2 + 0.009x - 0.0035$
Bone	$-2E\text{-}05x^2 + 0.0012x - 0.0089$

* The average weight of a rat is 165 gr. The standard weights of male and female are 73,000 and 60,000 grams, respectively

In order to absorb radiopharmaceuticals in the organs of the human body based on the animal model, a correction factor was used. Table 2 shows the information needed to calculate the correction factor. The information extracted for humans is based on ICRP and MIRD reports [24].

According to the cumulative activity in rat organs and the application of correction coefficients, the cumulative activity of organs in the patient's body was calculated after radiopharmaceutical injection. Table 3 shows the radiation dose of critical human organs from ^{99m}Tc-MIBI injection in the cardiac study. Based on the field study, the injection dose of radiopharmaceutical for cardiac perfusion using ^{99m}Tc-MIBI was between 25 and 30 mCi.

Table 2. Weight of critical organs in rats, humans and correction factor separately for men and women

Critical organs	Rats organ mass (gr)	Human organ mass (gr)		Organ correction factors*	
		Male	Female	Male	Female
Blood	2.45	5600	4100	5.17	4.61
Heart	0.51	330	250	1.45	1.34
Lung	0.90	500	420	1.26	1.29
Salivary glands & Thyroid	0.61	105	105	0.39	0.47
liver	2.26	1800	1400	1.80	1.71
Spleen	0.70	150	130	0.49	0.51
Kidney	1.00	310	275	0.70	0.76
Stomach	1.28	150	140	0.27	0.30
Muscle	2.00	29000	17500	32.83	24.11
Bone	0.64	10500	7800	37.30	33.71

*The average weight of a rat is 165 gr. The standard weights of male and female are 73,000 and 60,000 grams, respectively

Table 3. The absorbed dose per injection of unit activity in critical human organs from ^{99m}Tc-MIBI injection and the minimum and maximum absorbed doses from injection were 25 and 30 mCi, respectively

Critical organ	Absorbed dose / activity (mGy/MBq)		Absorbed dose [a] (Min.) (mGy)		Absorbed dose [b] (Max.) (mGy)	
	male	female	male	female	male	female
Blood	2.95E-04	2.62E-04	0.27	0.24	0.33	0.29
Heart	2.99E-03	2.75E-03	2.76	2.55	3.31	3.06
Lung	1.80E-03	1.84E-03	1.67	1.71	2.00	2.05
Salivary glands &Thyroid	2.20E-02	2.68E-02	20.36	24.77	24.48	29.72
Liver	1.12E-02	1.06E-02	10.40	9.84	12.48	11.81
Spleen	6.77E-03	7.14E-03	6.26	6.61	7.52	7.93
Kidney	1.98E-02	2.14E-02	18.32	19.77	21.98	23.73
Stomach	1.02E-03	1.16E-03	0.95	1.07	1.13	1.29
Muscle	5.64E-03	4.14E-03	5.22	3.83	6.26	4.59
Bone	2.29E-02	2.07E-02	21.22	19.18	25.47	23.02

In order to calculate the cumulative activity of the ^{99m}Tc-MIBI complex based on the diagrams drawn in Figure 1 in critical organs, the area below the curve surface of the diagrams was calculated. Table 1 shows the biodistribution equation of the diagrams in Figure 1 by organs. The proposed biodistribution Equations for each rat organs were obtained using the Trendline option (Polynominal) from Excel software.

The mean effective dose per unit of activity was 0.0062 mSv/MBq. Tissue weight factor reported in ICRP 106 was used to calculate the effective dose [2].

4. Discussion

In this study, the radiation dose of critical human organs was evaluated in a cardiac scan using a ^{99m}Tc-MIBI injection. The obtained values were based on measuring the biological distribution of radiopharmaceuticals in rats. ^{99m}Tc-MIBI is a cationic complex that accumulates in living myocardial muscle tissue after injection in proportion to local blood flow. After injection, it is rapidly purified from the blood and accumulates in muscle tissue, liver, kidneys, and in small amounts in the salivary and thyroid glands [25]. As shown in Table 3, the highest uptake of ^{99m}Tc-MIBI was in bone, salivary gland, thyroid glands, kidneys and liver, respectively. The biodistribution of radiopharmaceuticals in the study of cardiac nuclear medicine depends on the procedure model under rest or stress. In our study, the rats were inactive and the accumulation of radiopharmaceuticals was based on the rest model. Absorbed dose values in different studies show different values. In the study by Toohey *et al.* [26], the absorbed dose of the heart in a 25 mCi injection of ^{99m}Tc-MIBI was 1.2 mGy, while in our study the cardiac absorption dose of the same amount of activity was 2.21 mGy. The difference in the amount of absorbed dose depends on the type of radiopharmaceutical, factor S, the biological half-life of tissues, the method of biodistribution of radiopharmaceuticals in the body, and the method of calculation [6]. One of the differences is related to the injected dose of radiopharmaceuticals into the patient. In 2014, ^{99m}Tc-MIBI injected dose in a rest model heart study at 16 Canadian health centers was reported to be between 10 and 30 mCi with an average of 23.1 mCi and effective dose per unit of activity was reported to be 0.0090 mSv/MBq with a mean effective dose of 7.7 mSv [27]. In our study, the effective dose per unit of activity was 0.0062 mSv/MBq. In the ICRU report, the effective dose per unit of activity in the cardiac study in the rest model is 0.0085 mSv/MBq. In our study, the average effective dose was 6.3 mSv for both sexes. The mean effective dose limit in the ICRU report for the rest technique was 11.3 mSv [4]. Organ dose calculation from ^{99m}Tc-MIBI radiopharmaceutical injection based on direct measurement of radiopharmaceutical biodistribution in animal samples has rarely been performed. In several studies, different organs have been introduced as the most critical organ in the study of the heart with ^{99m}Tc-MIBI radiopharmaceutical. In our study, the kidneys, salivary glands, thyroid, and spleen were the most critical organs and in cardiac nuclear medicine

effective dose of these organs should be considered. The biodistribution curve of radiopharmaceutical in the spleen (Figure1b) is increasing during the study period and has not yet reached the absorption peak. This behavior indicates that the effective dose for the spleen was underestimated. In ICRU, the spleen shows the highest absorption after the kidney. In the Helal study [28], the highest uptake of radiopharmaceuticals occurred in the heart muscle and then in the spleen. Our study shows that the absorbed dose of blood and stomach wall has the lowest value. It seems that a detailed study of the cause of the difference in the radiation dose values of the target organs obtained in several articles is very necessary.

5. Conclusion

The organ dose in the human body was evaluated in a heart nuclear medicine study with ^{99m}Tc-MIBI based on an animal study. The kidneys, salivary glands, thyroid, and spleen had the highest dose in the study of the heart, and in optimizing the amount of activity injected into the body, the absorbed dose of these organs should be considered. The lowest dose was for blood and stomach wall. This study showed that the effective dose rate per unit of activity was about 0.0062 mSv/MBq, which is about 28% less than the values reported in the ICRU reference.

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