Original Article

Estimation of Organ-Absorbed Doses in Human from Gamma Rays of ^{99m}Tc-DTPA Radiopharmaceutical, Using the Animal Dissection Data

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Abstract

Introduction: Scintigraphy of renal system with radiopharmaceuticals extracts provides us with essential information as to assist the diagnosis and management of patients. In this research, effective doses of human's organs due to gamma-rays of 99mTc-DTPA are estimated using the animal dissection data.

Materials and Methods: In this study, the human absorbed and effective doses from ^{99m}Tc-DTPA are obtained from animal organs data, using medical internal radiation dosimetry (MIRD) method and MCNP simulation code. In each stage, three mice were injected and sacrificed, and then their organs were dissected and counted by well detector.

Results: The results of MIRD and MCNP simulation code indicated that the two mentioned methods are in agreement. Also, kidney (1.23E-03mGy/MBq), spleen (2.81E-03 mGy/MBq) and heart (2.75E-03 mGy/MBq) absorbed the most gamma dose compared to the other organs.

Conclusion: According to the results and comparison with ICRP data, animal dissection model can be a useful tool for internal absorbed dose estimation of renal radiopharmaceuticals.

Keywords: MCNP simulation code, MIRD method, ^{99m}Tc- DTPA, Effective dose

1. Introduction

The radiopharmaceuticals for studying the function and anatomy of renal can be categorized into three groups: first, the radiopharmaceuticals filtered by the glomerulus; second, the radiopharmaceuticals retained in the renal tubules via proximal tubule receptor-mediated endocytosis from the glomerular filtrate [1-3]; and third, the radiopharmaceuticals primarily secreted by the renal tubules via the organic anion transporter. ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 are filtered through the glomerulus. ^{99m}Tc-MAG3 and ^{131}I-iodohippurane are excreted by the renal tubules [1,2]. They are helpful in evaluating patients with diminished renal function and kidney transplants. ^{99m}Tc-MAG3 is both filtered and excreted, and that is why some radiologists prefer it to other radiopharmaceuticals [1-3]. ^{99m}Tc-DTPA is widely used in radiopharmaceutical kidney imaging but ^{99m}Tc-MAG3 is used more than ^{99m}Tc-DTPA for patients with suspected obstruction and impaired renal function [1-5]. ^{99m}Tc-DMSA and Glucoheptonate are accumulated in the cortex; hence, they are helpful in evaluating renal scarring from chronic infection, infarction, renal mass,

etc. ^{131}I-iodohippurane is a renal agent used in diagnostics of kidneys' malfunctions and renal tract obstructions. The renal excretion for this radiopharmaceutical is mainly through tubular secretion. However, ^{131}I is not near the optimal conditions because of its physical properties and hence the image quality and radiation seems to be a burden, delivering a high radiation dose [7,8]. Erbslöh- Möller et al. indicated that ^{131}I-hippuran renography has better sensitivity compared with ^{99m}Tc-DTPA scintigraphy for the purpose of diagnosing renovascular hypertension (RVH) [8]. ^{99m}Tc-DMSA as a static renal radiopharmaceutical is considered the reliable tool for investigating relative renal function and the most appropriate agent for renal cortical imaging. Radiopharmaceuticals can deliver radiation dose to organs because of the presence of their radioisotopes. Estimation of the absorbed dose from radiopharmaceuticals is an important part of the usage and development of novel agents. Many researches have been performed as for calculating the internally absorbed dose after radiopharmaceuticals' administration [12-18]. In 2014, the Shanehsazzadeh et al. have recently obtained and compared effective dose of different organs of body resulting from injection of two radiopharmaceuticals of ^{99m}Tc-Bombesin and ^{67}Ga-Bombesin [19]. In 2012, Shahbazi et al. determined the absorbed dose of different organs resulting from ^{99m}Tc-dioxide phosphene where the highest dose of 38.73E-4mGy/MBq was delivered to the kidney [17]. Angela Keleher et al. (2004) calculated the dose of 92.5MBq of ^{99m}Tc - sulfur colloid on pregnant women, with the highest dose calculated to the fetus as 7.74E-2mGy [19]. There are different methods for estimating the internal radiation dose from diagnostic and therapeutic radiopharmaceuticals. One of the most important methods is "Medical Internal Radiation Dose (MIRD)". This method is based on the absorbed fraction: it means that a fraction of emitted energy from source organs is absorbed on target organs [12]. Also, simulation with Monte Carlo method is another way. MCNP as a Monte Carlo code is used for calculating the absorbed dose. This is a general-purpose code that can be used for some particles transport [20]. The aim of this study is the estimation of human absorbed dose of ^{99m}Tc-DTPA resulting from 1 MBq after intravenous injection to mice, using MIRD and MCNP simulation code.

2. Materials and Methods

This study is divided into two sections: theoretical and experimental. In the experimental section, for preparing the ^{99m}Tc-DTPA, Technetium-99m was produced from the decay of ^{99}Mo on an aluminum oxide column in ^{99}Mo/^{99m}Tc generator. The ^{99m}Tc in the form of sodium pertechnetate solution was eluted by sterile NaCl (0.9 %w/v) at room temperature. After radiolabeling of DTPA with ^{99m}Tc, an activity of 3.7 MBq was injected via the tail vein. Mice experiments were completed in compliance with the regulations of our institution and with generally accepted guidelines governing such work. For this purpose, 3 time groups (each group consisting of 3 mice) is considered.

After 10, 30 and 120 min, the mice in groups of three animals were sacrificed, organs of interest were dissected, weighed and radioactivity was measured in a gamma well-type detector. The percentage of the injected dose per gram (% ID/g) was calculated for each tissue. Internally absorbed dose calculations were done based on the 0.14 MeV peak for ^{99m}Tc.

Absorbed dose on organs in overall is defined by following relation:

$$D = \frac{d\varepsilon}{dm} \qquad (1)$$

$d\varepsilon$: Average energy of ionizing radiation for dm

By considering the type of particle on creating biologic effects, equivalent dose is applied, which is equal to absorbed dose

multiplied by the radiation weighting factor.

$$H=DW \quad (2)$$

Table 1. Weighting factor of some radiations[12]

The type of radiation	**Radiation weighting factor**
Alpha particles	20
Beta particles	1
Gamma & X Ray	1

The effective dose is calculated by multiplying the equivalent dose (H) by a tissue weighting factor (W_T). Effective dose is a quantity that considers the effect of taking beams by various tissues, in addition to considering the role of different beams on emergence of biologic effects, and equals to multiplying equivalent dose in tissue weighting factor [21,22].

$$E=W_T*H \quad (3)$$

After preparation and injection of radiopharmaceuticals, animal studies were carried out in accordance with the UK Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations. The activity was measured with well-type counters before and after administration of the radiopharmaceutical. After injecting radiopharmaceutical to mice, they were sacrificed and their organs were dissected. Three samples from each organ were dissected, weighed and then counted to determine the percentage of injected dose per gram (which was equivalent to the percentage of injected activity per gram %IA/g: %ID/g); all the organ activity measurements were normalized to injected activity.

Activity concentration of radiopharmaceuticals at times (t) was calculated as the percentage of injected activity of each of organs [18, 23, 24]:

$$ID/g = \frac{A_{tissue}/M_{tissue}}{A_{injected}} \quad (4)$$

where A_{tissue} is the concentrated activity on sample tissue, M_{tissue} is the mass of sample tissue and $A_{injected}$ is the total injected activity to mice.

The dose of radiation delivered from a source tissue to a target tissue is dependent on the value of radioactivity in the source tissue and the time length of the radiopharmaceuticals resides in the source tissue. Due to the continuous uptake and elimination of the radiopharmaceutical administered to the living system and physical decay of the radionuclide, the radioactivity in each organ is dependent on time (function of time). The cumulated radioactivity, $\tilde{A}$, can be shown as eq. (5):

$$\tilde{A}_{h\,tissue} = \int_{t_1}^{\infty} A_h(t)\,dt \quad (5)$$

$A_h(t)$: activity of each tissue on time (t). $\tilde{A}$ accounts for the radioactivity in the tissue, and how long it resided in source tissue.

After calculating the activity for organs at different times, related activity curves were drawn for each. Then, using the curve-fitting method, cumulated radioactivity values were obtained.

For converting accumulated activity of mice organs to human organs, Sparks and Idogan method is used which is shown in eq. (6) [9,18]**:**

$$\tilde{A}_{humantissue} = \tilde{A}_{animaltissue} \times \frac{[Tissue mass/Body mass]_{human}}{[Tissue mass/Body mass]_{animal}} \quad (6)$$

Due to the length and attenuation between the source tissues and target tissues, a mere fraction of the energy emitted by the source tissue is absorbed by the target organ. This energy fraction needs to be quantified so that the total absorbed dose by the target tissue can be estimated.

The equation for absorbed dose in the MIRD system is shown as eq. (7):

$$S = \frac{k\sum_i n_i E_i \phi_i}{m} \quad (7)$$

where n_i is the number of radiations with energy E emitted per nuclear transition, E_i is the energy per radiation (MeV), ϕ_i is the fraction of energy absorbed in the target, m is the mass of target region (g or kg) and k is proportionality constant (rad-g/□Ci-hr-MeV or Gy-kg/MBq-sec-MeV).

Absorbed dose was calculated by using MIRD formula [18]:

$$D = \tilde{A}\, S \qquad (8)$$

$$\text{or} \quad D(r_k) = \sum_h \tilde{A}_h S(r_k \leftarrow r_h) \qquad (9)$$

where $D(r_k)$ is the absorbed dose of the target tissue (rad or Gy), $\tilde{A}_h$ is the accumulated activity in source tissue (□Ci-hr or MBq-sec) and $S(r_k \leftarrow r_h)$, called S factor, which is defined as the mean absorbed dose to the target region r_k per unit of accumulated activity in the source region r_h. The S factor represents the physical decay characteristics of the radioisotopes, the range of the emitted radiations, and the organ size. The S factors have been taken from the tables presented in the medical internal radiation dose No. 11 [15] and also available in http://doseinfo-radar.com/RADARphan.html.

By calculating the accumulated activity from eq.5 for mice and then converting it to human accumulate activity from eq.6, the absorbed dose taken from different organs can be calculated by eq.8. The calculated dose for each organ is obtained through the sum of absorbed doses from radiation, emitted from other organs in addition to the absorbed dose.

In continuation, The absorbed dose of different body organs were obtained by converting the mice results to the human and accumulating the activity through both methods. On the first stage, equivalent absorbed dose and effective absorbed dose of different organs after injection of radiopharmaceutical were obtained by using MIRD and S factor, which is shown as Tables 2 and 3.

For dose estimation by MCNP simulation code, the absorbed and effective doses of some organs such as lungs, liver, spleen, heart, stomach, pancreas, adrenal, intestine and kidneys are estimated within an adult male ORNL phantom (input file of ORNL phantom - adult male (Eckerman et al., 1996)). To that end, a grown male phantom consisting of soft tissue materials, bone tissue and lung tissue is applied. Tissues with accumulated activity are applied as the radioactive volume sources. MCNP as a Monte Carlo code needs the source for a problem to be specified in a user defined input file. In the source card, particle type, source position and distribution, energy, and direction of starting particles were specified. For simulation of our work, it is assumed that the radiopharmaceuticals were uniformly distributed throughout the organs. The radiopharmaceuticals used in this research emit gamma (^{99m}Tc) radiation. Then, human phantom was stimulated on MCNP code; the amount of effective absorbed dose of different organs for these radiopharmaceuticals is shown on Tables 2 and 3. To reduce the statistical error (below 5%), 1E7 particles were determined for NPS. The source energy was chosen based on the 0.14 MeV peak for ^{99m}Tc.

Tallies of F6 and *F8 can be applied for calculation of absorbed dose in MCNP code. In this simulation, both *F8 and F6 was used to calculate absorbed dose in the mentioned tissues (F6 tally only for gamma source was used).

3. Results

Figures 1-6 show the percentage of injected dose per gram at times of 10, 30 and 120 minutes after intravenous injection of ^{99m}Tc-DTPA on different organs of mice.

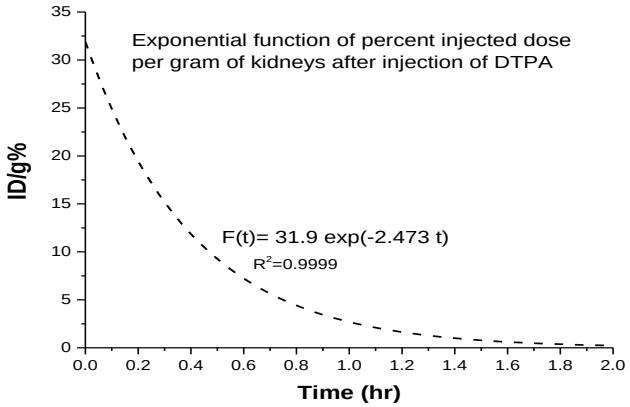

Figure 1. The clearance curves of kidneys after IV injection of 99mTc-DTPA The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g))

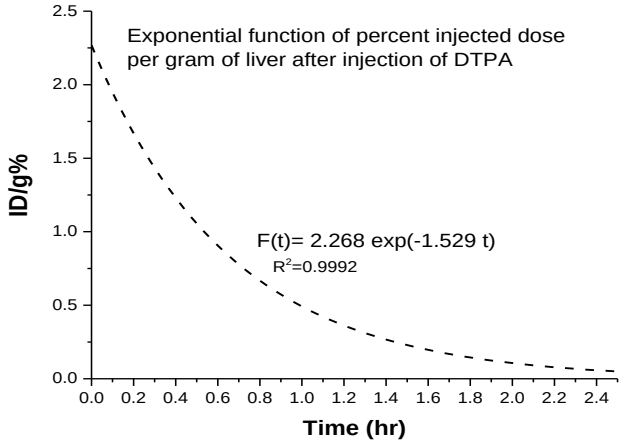

Figure 2. The clearance curves of liver after iv injection of 99mTc-DTPA. The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g))

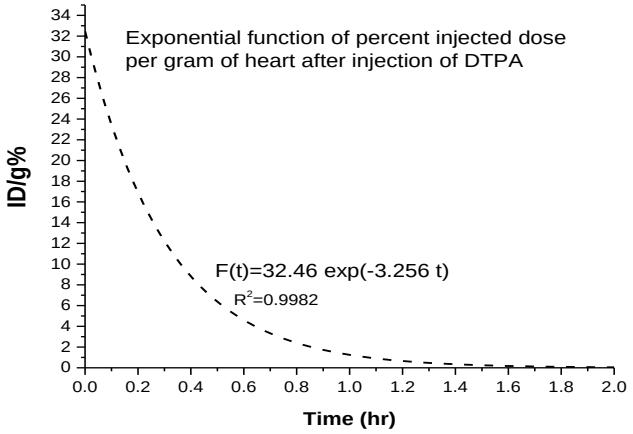

Figure 3. The clearance curves of heart after iv injection of 99mTc-DTPA. The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g)

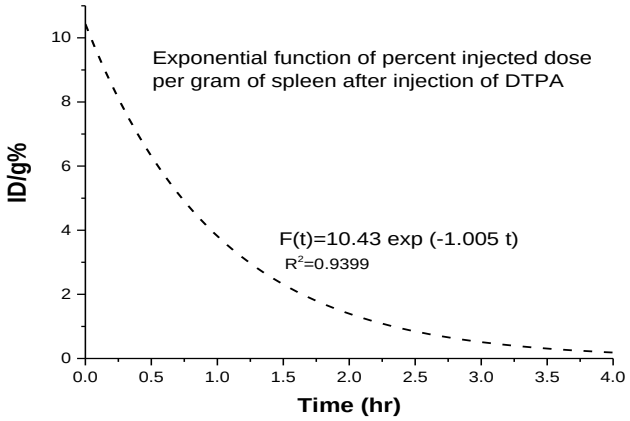

Figure 4. The clearance curves of spleen after iv injection of 99mTc-DTPA. The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g))

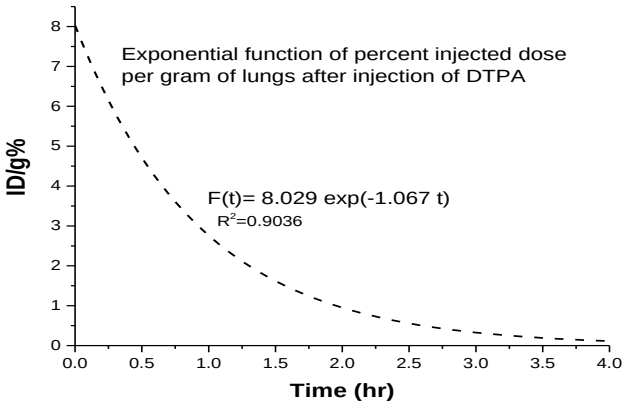

Figure 5. The clearance curves of lung after iv injection of *99mTc-DTPA*. The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g))

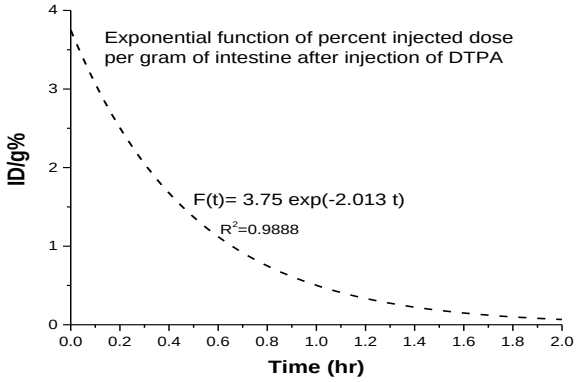

Figure 6. The clearance curves of intestine after iv injection of 99mTc-DTPA. The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g))

After calculating the absorbed dose by MIRD and MCNP methods, the amount of effective absorbed dose of different organs for this renal radiopharmaceutical was obtained. The results of both methods are indicated in Tables 2 and 3.

Table 2. Assessment of human effective dose based on mouse data after intravenous administration of 99mTc- DTPA using MIRD method and comparison with stabins's human data

Target organs	Mean estimated absorbed dose (mGy/MBq)	W_T	Mean effective absorbed dose (mSv/MBq)[a]	Human Absorbed Dose mGy/MBq (Stabin et al.[8])
Liver	4.79E-04	0.04	1.92E-05	1.80E-03
Intestine	3.54E-04	0.12	4.25E-05	8.50E-03
Pancreas	1.03E-03	0.01	1.03E-05	2.10E-03
Kidneys	1.23E-03	0.01	1.23E-05	5.70E-03
Spleen	2.81E-03	0.01	2.81E-05	1.90E-03
Heart	2.75E-03	0.01	2.75E-05	1.70E-03
Lungs	1.15E-03	0.12	1.38E-04	1.50E-03
Stomach	1. 2E-03	0.12	1.44E-04	1.90E-03
Adrenals	6.98E-04	0.01	6.98E-06	2.00E-03

[a] If injected 1MBq activity of radio-tracer.

Table 3. assessment of human effective dose based on mouse data after i.v administration of 99mTc- DTPA using MCNP method.

Target organs	Mean estimated absorbed dose (mGy/MBq)	W_T	Mean effective absorbed dose (mSv/MBq)[a]	Human Absorbed Dose mGy/MBq (Stabin et al.[8])
Liver	2.65E-04	0.04	1.06E-05	1.80E-03
Intestine	3.49E-04	0.12	4.19E-05	8.50E-03
Pancreas	1.15E-03	0.01	1.15E-05	2.10E-03
Kidneys	1.34E-03	0.01	1.34E-05	5.70E-03
Spleen	3.46E-03	0.01	3.46E-05	1.90E-03
Heart	2.08E-03	0.01	2.08E-05	1.70E-03
Lungs	3.12E-03	0.12	3.74E-04	1.50E-03
Stomach	1.56E-03	0.12	1.88E-04	1.90E-03
Adrenals	6.62E-04	0.01	6.62E-06	2.00E-03

[a] If injected 1MBq activity of radio-tracer.

4. Discussion

Labeling of diethylenetriaminepentaacetic acid (DTPA) with Tc-99m, sodium pertechnetate results in the preparation of radiopharmaceutical 99mTc-DTPA. The individual renal mode of clearance for this radiopharmaceutical promotes its usage in scintigraphy study of kidneys. The IV administered 99mTc-DTPA (with a half-life of 70 minutes) is filtered by the renal glomeruli, thereby allowing assessment of glomerular filtration rate (GFR). So, it is the most suitable substance for measuring glomerular filtration (GFR) and good imaging of renal parenchyma.

The use of a radiopharmaceutical requires calculation of its biodistribution in some models prior to its clinical applications [25-29]. In this study, internal radiation dosimetry of the well-known renal imaging agent, 99mTc-DTPA, was calculated and compared (based on mouse data) through two important methods. Based on the assumption that the biodistribution of radiopharmaceuticals could be similar in mouse and in human (ICRP 103), assessment of absorbed dose in human body from small animal such as mouse may be useful for accelerating the planning of new radioactive compounds to be used in clinical experiments (recommendations of ICRP 62). There are various methods to estimate the absorbed dose after radiopharmaceuticals injection, such as Monte Carlo Codes, MIRD, etc.

The results of ^{99m}Tc-DTPA distribution in body using the two mentioned methods showed that the absorbed dose in kidney (1.23E-03mGy/MBq), spleen (2.81E-03

mGy/MBq) and heart (2.75E-03 mGy/MBq) are considerable. This may be related to the chemical structure and stability of radiopharmaceuticals.

The results of MIRD and MCNP code show a decent agreement for 99mTc-DTPA, and the difference between absorbed doses in more organs was lower than 10 percent.

The mouse model dosimetry was not in good agreement with Stabin's dosimetry data. It can be due to different uncertainties in both methods, different measurement instruments, excluding the rest of the rays (only gamma energy=0.14 MeV is used), mouse to human conversion factor (Sparks and Idogan equation), difference between human and mouse tissues geometry, etc. According to the mean effective half-life of radiopharmaceutical which is reported to be short in body, it was obvious that all the injected activity should be cleared from the main organs in short time and it would be better to have more time points before one-hour to get better results for calculating the cumulative activity; consequently, the selection of low time points because of some limitations might be one of the reasons of difference between mouse and Stabin's model results.

In general, there is a good agreement between MCNP and MIRD results for the mentioned radiopharmaceutical.

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Conflict of interest

The authors declare no conflict of interest.

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