Assessment of Internal Absorbed Dose in the Human Abdominal Organs from Two Renal Radiopharmaceuticals Based on Experimental Mouse Data

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Research Article

Abstract

Background: Radiopharmaceuticals have several applications in medicine such as imaging and therapeutic processes. Radiopharmaceutical renal scintigraphy presents important functional data to assist in the diagnosis and management of patients.

Methods and findings: In this research, the human effective dose from two important renal imaging agents (^{99m}Tc- MAG3 and ^{131}I-Hippuran) is estimated, after injection of those in animal body. Effective dose in human body is estimated using MIRD method and MCNP simulation code (with F6 and *F8 tally) for different organs. Sources with energies of 140keV (gamma) for 99mTc and 364 keV (gamma), 192 keV (average energy of beta) for ^{131}I are considered. The results of ^{99m}Tc-MAG3 and ^{131}I-Hippuran dosimetry showed that the lung and stomach (for ^{99m}Tc-MAG3) and stomach and lung (for ^{131}I-Hippuran) had the most effective dose relative to the other organs respectively.

Conclusion: There is no good agreement between mouse model and Stabin's human model for ^{131}I-Hippuran.

Keywords: MCNPX simulation code; MIRD method; ^{99m}Tc- MAG3; ^{131}I-Hippuran; Effective dose.

1. Introduction

Radiopharmaceuticals are applied in nuclear medicine for therapy and diagnosis of disease and organ function. The radiopharmaceuticals can enter the human body as radioisotopes alone or radioisotopes connected to different chemical compounds. Some radiopharmaceuticals are used for renal function and anatomy. The radiopharmaceuticals for investigation of renal function and structure can be divided into three categories: 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, and third, the radiopharmaceuticals primarily secreted by the renal tubules *via* the organic anion transporter [1]. ^{131}I-Hippuran and ^{99m}Tc-MAG3 are two important radiopharmaceuticals in renal scintigraphy. ^{99m}Tc-MAG3 is a renal tubular agent which was introduced in 1986 as an alternative for the use of ^{131}I-Hippuran with similar pharmacokinetic and human renogram pattern. ^{99m}Tc-MAG3 is highly protein-bound and is removed from the plasma primarily by the organic anion transporter 1 [2]. ^{99m}Tc-MAG3 is used more than ^{99m}Tc-DTPA for patients with suspected obstruction and impaired renal function (IRF) and is applied in almost 70% of the renal scans performed in the US [1,3,4].

^{131}I-iodohippurane is a radiopharmaceutical used in diagnostics of kidneys malfunction and renal tract obstructions. After injection, ^{131}I-iodohippurane is excreted by the renal system rapidly. The maximum uptake in renal system occurs almost within 2 to 5 minutes of injection. The peak of uptake often depends on the nature of the kidneys diseases, the patient hydration and extent of renal impairment. More than 60% of the mentioned radiopharmaceutical binds reversibly with plasma proteins. The renal excretion for this compound is mainly by tubular secretion (80%) and glomerular filtration (20%). The clearances of these renal radiopharmaceuticals are often characterized as the effective renal plasma flow. ^{131}I-Hippuran is cleared from plasma by tubular secretion. However,^{131}I is far from optimal with regard to physical properties and hence to image quality and radiation burden. Preliminary studies of ^{99m}Tc-MAG3 in normal volunteers indicated that plasma clearance

was less than that of ^{131}I-Hippuran [5]. ^{131}I-Hippuran has the poor imaging characteristics and deliver a high radiation dose. The study by Erbslöh- Möller et al. [6], demonstrated a better sensitivity of ^{131}I-hippuran renography than ^{99m}Tc-DTPA scintigraphy to diagnose renovascular hypertension (RVH). Although the clearance of ^{99m}Tc-MAG3 is only 50%–60% that of OIH (^{131}I-Hippuran), the ^{99m}Tc-MAG3 clearance is highly correlated with the clearance of OIH, and the ^{99m}Tc-MAG3 clearance can be used as an independent measure of renal function [7,8].

The body receives radiation dose from the radiopharmaceuticals. Appraising the internal radiation dosimetry of radiopharmaceuticals is an essential part of the usage and development of novel radiopharmaceuticals. Many studies have been completed for calculation of the internal absorbed dose after injection of radiopharmaceuticals in body [9-15]. In 2004, Angela Keleher et al. calculated the dose of 92.5MBq of [99m]Tc - sulfur colloid on pregnant women, the highest dose calculated to the fetus was 7.74E-2mGy [16]. In 2012, Shahbazi et al. determined the absorbed dose of different organs resulting from ^{99m}Tc-dioxide phosphene where the highest dose of 38.73 E-4mGy/MBq was delivered to the kidney [14]. In 2014, the authors have recently calculated and compared effective dose of different organs of body resulting from injection of two radiopharmaceuticals of ^{99m}Tc-Bombesin and ^{67}Ga-Bombesin [15].

There are several methods to calculate the internal absorbed dose of radiopharmaceuticals. One of the methods is "Medical internal radiation dose (MIRD)". MIRD has offered a method for calculation of gamma beam energy on organs and tissues. This method is based on absorbed fraction; it means that a fraction of emitted energy from source organs is absorbed on target organs [9]. MCNP code is a second method for calculating internal dose of body. MCNP is a general-purpose Monte Carlo N-Particle code that can be used for some particles transport. Specific areas of application include, but are not limited to, radiation protection and dosimetry, radiation shielding, radiography, medical physics etc. The code treats an arbitrary three-dimensional configuration of materials in geometric cells bounded by first-and second-degree surfaces and fourth-degree elliptical tori [17].

The purpose of this research is the calculation and comparison of human internal absorbed dose of two renal radiopharmaceuticals ([99m]Tc- MAG3 and ^{131}I-Hippuran) resulting from 1 MBq after intravenous injection to mice.

Materials and Methods

[99m]Tc was prepared from the decay of [99]Mo on an aluminum oxide column in a bench-top generator.

The ^{99m}Tc was eluted from the generator in sterile NaCl (0.9% w/v) at room temperature in the form of sodium pertechnetate solution. Internal dosimetry calculations were done based on the 140 keV peak for 99mTc and 364 keV (gamma), 192 keV (average energy of beta) for 131I.

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

$$D = \frac{d \in}{dm} \tag{1}$$

$d\,\varepsilon$: 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.

$$H = DW \tag{2}$$

The effective dose is calculated by multiplying the equivalent dose (H) by a tissue weighting factor (WT). Effective dose, is a quantity that in addition to considering role of different beams on emergence of biologic effects, also considers the effect of taking beams by various tissues and it is equal to multiply of equivalent dose in tissue weighting factor [18,19].

$$E = WT*H \tag{3}$$

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 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 [15,20,21].

$$ID/g = \frac{A_{tissue}/M_{tissue}}{A_{injected}} \tag{4}$$

Where A tissue is the concentrated activity on sample tissue, M tissue is mass of sample tissue and A injected is total injected activity to mice.

After that, the activity accumulation in source organs is calculated by following method.

2.1 Cumulated radioactivity and dose calculation

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 eqn. (5):

$$A_{h\,tissue} = \int_{t]} A_h(t)\,dt \qquad (5)$$

Ah (t): activity of each tissue on time (t). Ã accounts for the radioactivity in the tissue, and how long it resided in source tissue.

After calculation the activity for organs at different times, related activity curves were drawn for them. 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 eqn. (6) [6,15]:

$$\tilde{A}_{human\,tissue} = \tilde{A}_{animal\,tissue} \times \frac{Tissue\,mass\,/\,Body\,mass_{human}}{Tissue\,mass\,/\,Body\,mass_{animal}} \qquad (6)$$

Due to the length and attenuation between the source tissues and target tissues, just a 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 eqn. (7)

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

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/µCi-hr-MeV or Gy-kg/MBq-sec-MeV).

Absorbed dose was calculated by using MIRD formula [15];

$$D = \tilde{A}S \;or\; D(r_k) = \sum_h \tilde{A}_h S(r_k \leftarrow r_h) \qquad (8)$$

Where D(rk) is absorbed dose of the target tissue (rad or Gy), ˜h is the accumulated activity in source tissue (µCi-hr or MBq-sec) and S (rk ←rh) called S factor which is defined as the mean absorbed dose to the target region rk per unit accumulated activity in the source region rh. 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 [12] and also available in http://doseinfo-radar.com/RADARphan.html. Figure 1 shows a sample of source (Heart) and target (Intestine) tissues in MIRD model.

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

In this study, specific absorption fraction for 10 source and target organs (lungs, Liver, spleen, heart, stomach, pancreas, adrenal, large and small intestines and kidneys) is calculated within an adult male MIRD phantom which is written on 1996 by researchers of Hang Yang University of South Korea, is used. In this problem, MIRD phantom of a grown male consisting of soft tissue materials, bone tissue and lungs tissue is used. The tissues with absorbed activity are applied as the radioactive volume sources. Source energies of 0.14MeV for 99mTc and 364 keV (gamma), 192 keV (beta) for 131I and F6 and *F8 tallies were used for calculating internal absorbed dose. After injecting each of the radiopharmaceuticals, the mice were sacrificed and their organs dissected. A gamma counter was used to determine the percentage of injected dose per gram of organs at different times.

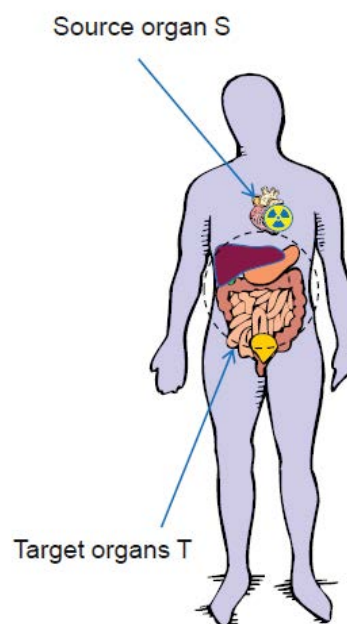In continuation, by converting the mice results to the human and having accumulated activity using

Figure 1. A sample of source (Heart) and target (Intestine) tissues.

two methods, absorbed dose of different organs of body were obtained. On first stage by using MIRD and S factor, equivalent absorbed dose and effective absorbed dose of different organs after injection MAG3 and IOH were obtained which is shown on Tables 1-3.

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) and beta-gamma (^{99m}Tc, $1^{31}I$) radiation. Since, Beta particles emitted from ^{131}I have a broad energy spectrum from zero to the maximum energy so in this simulation the mean beta energy of beta particles was applied.

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).

Then human phantom was stimulated on MCNP code and the amount of effective absorbed dose of different organs for these radiopharmaceuticals was shown in Tables 4 and 5. To reduce the statistical error (below 5%), 1E7 particles were determined for NPS. A sample of geometry of Human body, with

volume source located in liver tissue (planes xy and xz) is shown in Figure 2.

2. Results

In Figures 3-8 shows the percentage of injected dose per gram at times of 10, 30 and 120 minutes

Table 3. assessment of human effective dose based on mouse data after i.v administration of 131I-Hippuran using MIRD method and comparison with stabins's human data.

Target organs	Estimated absorbed dose	WT	Effective absorbed[a]	Human Absorbed Dose mGy/MBq (Stabin et al.[5])
Liver	8.12E-04	0.04	3.25E-05	1.70E-03
Large Intestine	1.04E-03	0.12	1.24E-04	8.00E-03
Pancreas	1.02E-03	0.01	1.02E-05	2.10E-03
Kidneys	7.80E-03	0.01	7.80E-05	4.50E-02
Spleen	2.52E-02	0.01	2.52E-04	2.00E-03
Heart	2.50E-02	0.01	2.50E-04	9.00E-04
Lungs	1.36E-02	0.12	1.63E-03	7.70E-04
Stomach	2.41E-02	0.12	2.89E-03	2.10E-03
Adrenals	7.83E-04	0.01	7.83E-06	2.10E-03

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

Table 4. Assessment of human effective dose based on mouse data after i.v administration of ^{99m}Tc- MAG3 using MCNP method.

Target organs	Estimated absorbed[a]	WT	Effective absorbed dose
Liver	1.06E-04	0.04	4.24E-06
Large Intestine	3.35E-04	0.12	4.02E-05
Pancreas	3.02E-04	0.01	3.02E-06
Kidneys	1.16E-03	0.01	1.16E-05
Spleen	9.33E-04	0.01	9.33E-06
Heart	2.45E-04	0.01	2.45E-06
Lungs	5.93E-04	0.12	7.12E-05
Stomach	3.70E-04	0.12	4.44E-05
Adrenals	1.76E-04	0.01	1.76E-06

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

Table 1. Weighting factor of some radiations.

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

Table 2. Assessment of human effective dose based on mouse data after intravenous administration of 99mTc-MAG3 using MIRD method and comparison with stabins's human data.

Target organs	Estimated absorbed dose (mGy/MBq)	WT	Effective absorbed dose (mSv/MBq)[a]	Human Absorbed Dose mGy/MBq (Stabin et al.[5])
Liver	1.40E-04	0.04	5.58E-06	3.50E-04
Large Intestine	2.94E-04	0.12	3.53E-06	2.10E-03
Pancreas	2.03E-04	0.01	2.03E-06	4.50E-04
Kidneys	1.04E-03	0.01	1.03E-05	4.10E-03
Spleen	7.49E-04	0.01	7.49E-06	4.10E-04
Heart	3.23E-04	0.01	3.23E-06	1.80E-04
Lungs	2.23E-04	0.12	2.68E-05	1.50E-04
Stomach	2.81E-04	0.12	3.38E-05	4.50E-04
Adrenals	1.96E-04	0.01	1.96E-06	4.40E-04

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

Table 5. Assessment of human effective dose based on mouse data after *i.v* administration of 131I-Hippuran using MCNP method.

Target organs	Estimated absorbed[a]	WT	Effective absorbed dose
Liver	7.78E-04	0.04	3.11E-05
Large Intestine	1.45E-03	0.12	1.74E-04
Pancreas	1.95E-03	0.01	1.95E-05
Kidneys	9.16E-03	0.01	9.16E-05
Spleen	2.96E-02	0.01	2.96E-04
Heart	2.71E-02	0.01	2.71E-04
Lungs	1.08E-02	0.12	1.30E-03
Stomach	5.13E-02	0.12	6.16E-03
Adrenals	1.00E-03	0.01	1.00E-05

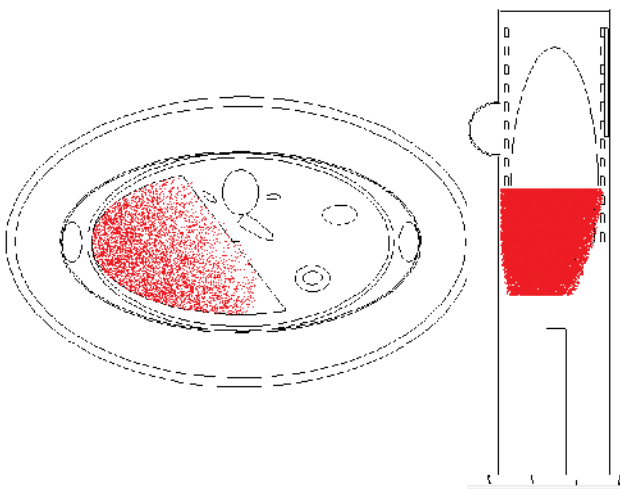[a]If injected 1MBq activity of radio-tracer.

Figure 2. A transverse and sagittal slice of the MCNP human body geometry.
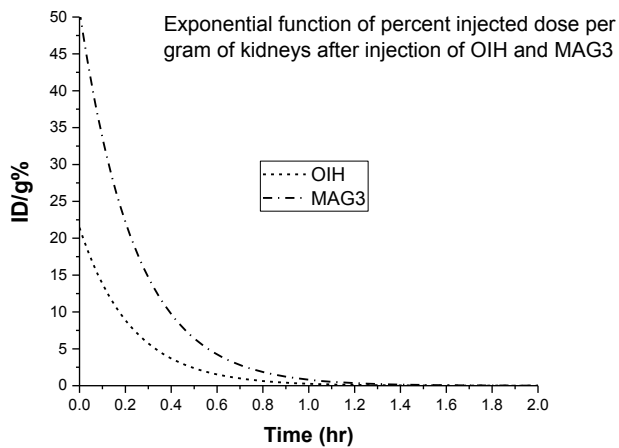

Figure 3. The clearance curves of kidneys after iv injection of MAG3 and OIH. The horizontal axis is displayed as hours post injections. Data are presented as mean + SD and the mean values as the percentage of administered activity per gram (%ID/g).
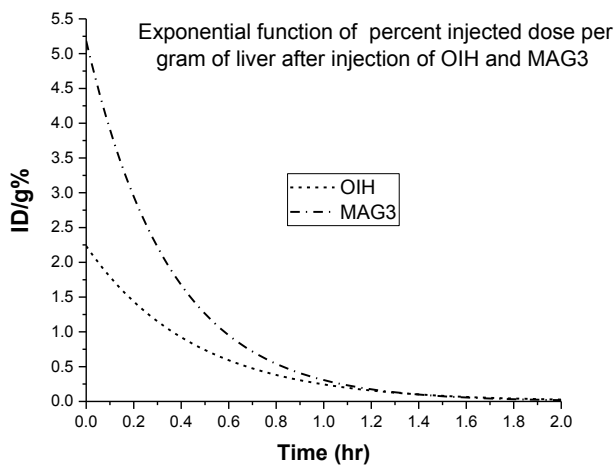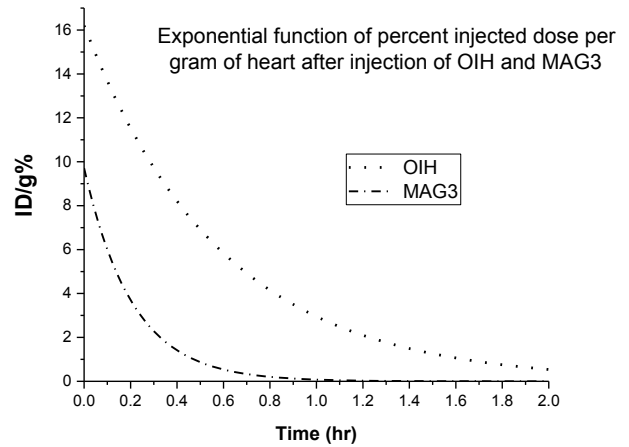

Figure 4. The clearance curves of liver after iv injection of MAG3 and OIH. The horizontal axis is displayed as hours post injections. Data are presented as mean + SD and the mean values as the percentage of administered activity per gram (%ID/g).

Figure 5. The clearance curves of heart after iv injection of MAG3 and OIH. The horizontal axis is displayed as hours post injections. Data are presented as mean + SD and the mean values as the percentage of administered activity per gram (%ID/g).
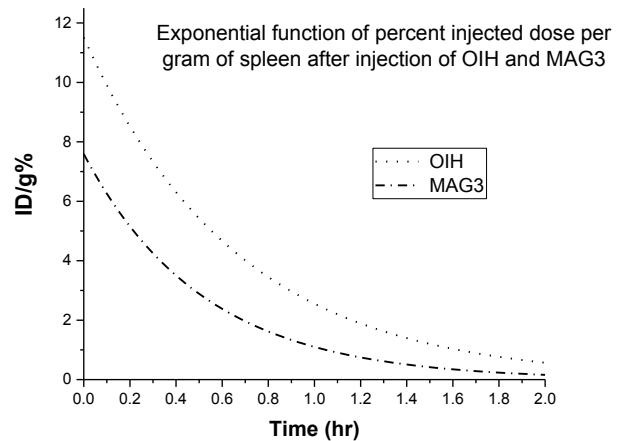

Figure 6. The clearance curves of spleen after iv injection of MAG3 and OIH. The horizontal axis is displayed as hours post injections. Data are presented as mean + SD and the mean values as the percentage of administered activity per gram (%ID/g).
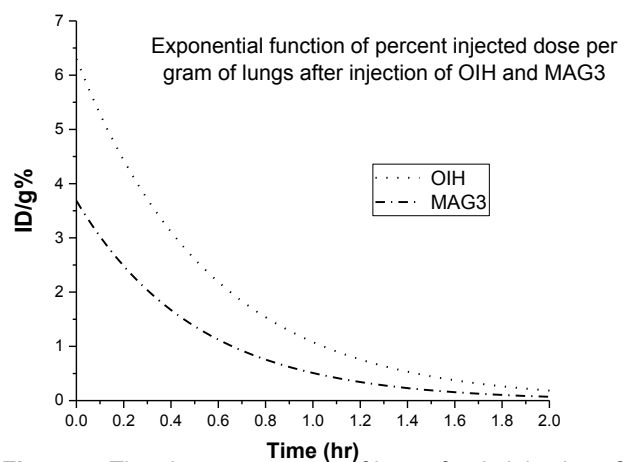

Figure 7. The clearance curves of lung after iv injection of MAG3 and OIH. The horizontal axis is displayed as hours post injections. Data are presented as mean + SD and the mean values as the percentage of administered activity per gram (%ID/g).

Figure 8. The clearance curves of intestine after iv injection of MAG3 and OIH. The horizontal axis is displayed as hours post injections. Data are presented as mean + SD and the mean values as the percentage of administered activity per gram (%ID/g).
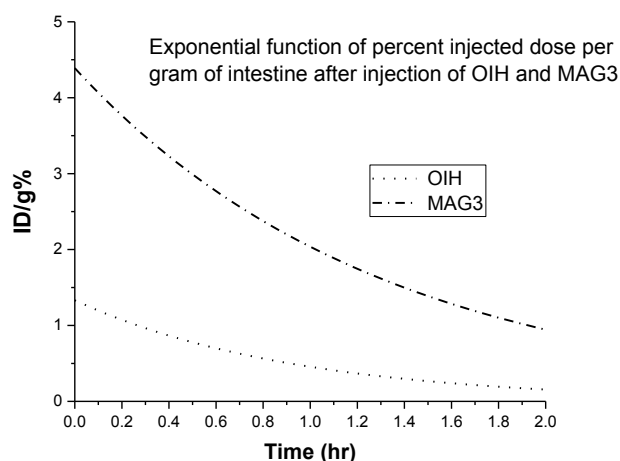
after intravenous injection of ^{99m}Tc-MAG3 and OIH on different organs of mice.

After calculation of absorbed dose by MIRD and MCNP methods, the amount of effective absorbed dose of different organs for these radiopharmaceuticals was obtained. The results of both methods are compared in Tables 1-5. Tables 2 and 4 show the assessment of human effective dose from mouse data after *i.v* administration of [99m]Tc- MAG3. Tables 3 and 5 show the assessment of human effective dose from mouse data after *i.v* administration of ^{131}I-Hippuran.

3. Discussion

Radiopharmaceutical renal studies provide information on renal function and structure. The information extracted from the study depends on the biological properties of the radiopharmaceuticals. Two important radiopharmaceuticals for renal system study are [99m]Tc- MAG3 and 1[31]I-Hippurane. ^{99m}Tc-MAG3 was introduced by Fritzberg et al. [22,23]. The biological characteristics of the ^{99m}Tc-MAG3 are somewhat different from those of ^{131}I-Hippurane which has considerable characteristics as effective renal plasma flow radio-agent [24]. However, ^{99m}Tc-MAG3 is now widely applied as an alternative to ^{131}I-Hippurane for the investigation of nephrological diseases.

In this study, internal radiation dosimetry of the two mentioned renal imaging agents were calculated and compared (based on mouse data). The use of a radiopharmaceutical requires calculation of its biodistribution in animal models prior to its clinical applications [15,25,26], based on the assumption that the biodistribution could be similar in mice and

in man (consistent with the recommendations of ICRP 103). Additional assessment of absorbed dose in human body from small animal such as mice 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 MIRD, Monte carlo methods, image based dosimetry, etc.

Internal absorbed dose was calculated by using MIRD method and MCNPX simulation code, from injection of [99m]Tc- MAG3 and ^{131}I-Hippuran radiopharmaceuticals on human organs resulted from accumulation of radiopharmaceutical on organs of lungs, Liver, spleen, heart, stomach, pancreas, adrenal, large and small intestines and kidneys based on distribution of radiopharmaceutical on normal mice.

The results of ^{99m}Tc-MAG3 and ^{131}I-Hippuran distribution in body showed that the absorbed dose in spleen, lung, heart and stomach are considerable. This may be related to the chemical structure and stability of radiopharmaceuticals. The highest effective doses on MIRD and MCNP method are related to stomach and lung after injection of 1 MBq of radiopharmaceutical (^{131}I-Hippuran). The obtained results from MIRD method were in line with MCNP results, and the difference between absorbed dose in each organ was smaller than 10 percent.

According to the results, the mouse model dosimetry (MIRD method) was not in good agreement with Stabin's dosimetry data. It can be due to different uncertainties in both methods, small organs of mouse, different measurement instruments etc. Based on equation 6, one of the factors of the difference the obtained results and Stabil's results could be due to mouse to human conversion factor (Sparks and Idogan equation). Another reason for the differences between our results and Stabin's results might be because of the difference between human and mouse tissues structure. According to the mean effective half-life of both radiopharmacuticals 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 calculationg the cumulative activity, therefore, 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.

The difference between the dosimetry results (Mouse model and Stabin's model) for ^{131}I-Hippuran is greater than ^{99m}Tc-MAG3. The high energy gamma and beta of ^{131}I in comparison with the gamma energy

of ^{99m}Tc as well as the small organs of the mouse can be the important factors in this difference.

In general, dosimetry results of both mentioned radiopharmaceuticals show that stomach and lung received the high effective absorbed dose among under risk organs after imaging with ^{99m}Tc- MAG3 and ^{131}I-Hippuran. Also ^{99m}Tc-MAG3 radiopharmaceutical is a better choice relative to ^{131}I-Hippuran for renal imaging in terms of dosimetry considerations. In addition, there is no good agreement between mouse model and Stabin's human model for ^{131}I-Hippuran.

4. Conflict of Interest

The authors declare that they have no conflict of interest.

5. Financial Support

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