Original Article

Comparison of estimated human dose of 111 In-rituximab by MCNPX code and MIRD method based on mice data

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Abstract

Introduction: Radiopharmaceuticals are widely used in modern treatment of cancer. The injection of radiopharmaceuticals into the patient's body and its accumulation in target tissue is expected to have the highest therapeutic effect on target tissue. The purpose of this study is to calculate the effective absorbed dose of labeled 111 In-rituximab in human body based on mice biodistribution data through MCNPX code and MIRD method.

Materials and Methods: In this investigation, the accumulated activity was first computed for mice source organs; then, it was converted into accumulated activity for human source organs via Sparks and Aydogan formula. After that, the equivalent and effective dose were calculated using MCNPX code and the Medical Internal Radiation Dose (MIRD) method.

Results: The results of the effective absorbed dose in human body showed that the highest absorbed dose concentrated in the lung (3.36E-04 Sv/MBq), and the organs that received the next highest doses are kidney (2.29E-04 Sv/MBq), spleen (1.57E-04 Sv/MBq), pancreas (1.19E-04 Sv/MBq) and heart (6.73E-05 Sv/MBq). Although our results were different, they were in good agreement with the literature on this subject.

Conclusions: According to the results of the study, as the effective absorbed dose using MIRD method indicates, the highest received doses were identified to be in lung, kidney, spleen, pancreas, heart, stomach, liver and intestine, in descending order.

Keywords: Indium-111, Rituximab, Effective absorbed dose, Monte Carlo simulation, MIRD method

1. Introduction

Radionuclides are comprised of two components: a chemical component and a radioisotope component [1]. After injection and accumulation in various organs of the body, radionuclides are excreted from the body through metabolic processes after a given time [1, 2]. Application of radioisotopes in medicine includes two important parts of diagnostic and therapeutic. About more than 90 percent of radioisotopes are used in cancer diagnosis

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and the remaining 10 percent in cancer therapy. Gamma emitter radioisotopes are used in cancer diagnosis because gamma ray has the high penetration and low uptake characteristic in tissues, whereas alpha and beta emitters are used in cancer treatment because the alpha and beta particles have high linear energy transfer (LET) [3-5]. Important diagnostic radiopharmaceuticals such as 99mTc, 111In, 18F, 131I, 68Ga are widely used either individually or in conjunction with some chemical molecules in many diseases [6, 7]. Important therapeutic radiopharmaceuticals such as 188Re and 177 Lu are used in bone metastases and metastatic pain, respectively [8-10]. Indium-111 is one of the well-known and most widely used radioisotopes in nuclear medicine for diagnostic purposes. By binding to a chemical molecule, this radioisotope is individually used as a radiopharmaceutical. Patrick et al. labeled trastuzumab with 111In for breast cancer as an agent for growth factor receptor 2-posetives [11]. Moreover, a number of studies have been done on labeling with radioisotope and their dosimetric study. Shirmardi et al. evaluated 67Ga-DOTA-Bombesin (7-14) for agent diagnosis of GRP receptor-positive tumors [12]. In addition, Shanesazzadeh et al. assessed effective absorbed dose of 67Ga and 99mTc-labeled bombesin (BBN) in various human organs [13]. 111In-rituximab, as a diagnostic and therapeutic radiopharmaceutical, is composed of two parts: 111In and antibody (Rituximab). 111In with a half-life of 2.80 days emits two gamma rays with energies of 245.4 and 171.3 keV as well as beta rays with energies of 6.8 and 25.9 keV [14]. Rituximab is a monoclonal antibody recognizing CD20 surface cell on more than 80% of NHLs [15]. To date, many studies about rituximab have been undertaken. David G. et al. and Maloney et al. did research into the treatment of patients with relapsed Low-Grade Non-Hodgkin's Lymphoma with IDEC-C2B8 (rituximab) Anti-CD20 Monoclonal Antibody [16]. Rituximab was initially used as a monoclonal antibody for treating patients with oncological problems and decreasing malignant cancer cells through a connection with CD20 positive [17]. In addition, the monoclonal antibodies ligation with CD20 operate apoptosis of malignant human B Cells and thereby abatement tumor regressions for mouse models and clinical experiments [18]. Other antibodies are polyclonal antibodies, a mixture of monoclonal antibodies which are produced against various multiple epitopes on the antigen surface. For cancer treatment, there is a need for antibodies that are produced from a specific clone called monoclonal. However, new recombinations of Polyclonal antibodies are used for cancer therapy [19]. Vast application of Polyclonal Antibodies includes identification, isolation, modification, and destruction. Other benefits of function antibodies are gained through conjugation to immunotoxins, radionuclides or enzymes to the molecule with diagnostics and therapeutics purposes, considering the responsibility of immunology and antibody structure and function[20]. This study was an attempt to calculate the delivered dose and the effective absorbed dose (Sv) of 111In-rituximab for various organs in human abdomen, employing simulation code and MIRD analytical method.

2. Materials and Methods

Absorbed dose calculation

The radiation absorbed dose in target organ was calculated by Equation (1).

$$D(r_k) = \sum_h \tilde{A}_h S(r_k \leftarrow r_h) \quad (1)$$

where $D(r_k)$ is the absorbed dose in target organ, $\tilde{A}_h$ is the accumulated activity in source organ which underwent change due to factors such as radiopharmaceutical absorption, biological excretion, and physical decay. The S factor is the mean

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absorbed dose in target organ per unit cumulated activity in the source organ[21, 22].

Measurement of activity

The accumulated activity in source organ(r_h) was calculated by Equation (2).

$$\tilde{A}_h = \int_0^{\infty} A(t)dt \quad (2)$$

where $\tilde{A}_h$ is the activity at time t for source organ(r_h). The accumulated activity in different organs was estimated based on the gathered biodistribution data in mice which received 111In-rituximab and were killed at 4, 24, 48 and 96h after injection. Then, the amount of the accumulated activity in the source organs was estimated by curves for each organ and computing the area under the curves for various organs[23].

The accumulated activity in human organs was estimated using Sparks and Aydogan method [24]according to Equation 3.

$$\tilde{A}_{humanorgan} = \tilde{A}_{animalorgan} \frac{organmass_{human} / bodymass_{human}}{organmass_{animal} / bodymass_{animal}} \quad (3)$$

Calculation of effective absorbed dose

The effective absorbed dose of each organ was calculated by Equation 4.

$$E = \sum_T W_T H_T \quad (4)$$

where HT is the equivalent dose in organ and WT is the tissue-weighting factor according to ICRP 106 [25].

MCNPX code

The MCNPX code is a general purpose Monte Carlo radiation transport code that tracks all particles such as neutron, proton, and photonuclear libraries for up to 150 MeV energies. Dose assessment in medical physics is well-known for applications of the code, especially in proton and neutron therapy. In this study, the geometry of source organ was accurately defined and the changes related to the geometry of the source organ and the target organ, particle type, particle energy, and the percentage of particle decay were determined based on F6 ($\frac{MeV}{gr}$) in the data card simulation code program. The distribution of activity was assumed to be of uniform in the source organs. MIRD-ORNL-MALE phantom was utilized to calculate the absorbed dose with MCNPX code[26].

3. RESULTS

The non-decay corrected clearance curve for source organs of the mice's body organs are illustrated in Figure 1[27]. Table 1 indicates estimation of equivalent absorbed dose and effective absorbed dose measured by MCNPX code and MIRD method based on bio-distribution mouse data. According to our estimation using by MCNPX code, the highest effective absorbed dose is for 111 In-rituximab in the lung (3.36E-04 Sv/MBq), and the organs that received the next highest doses are kidney (2.29E-04 Sv/MBq), spleen (1.57E-04 Sv/MBq), pancreas (1.19E-04 Sv/MBq) and heart (6.73E-05 Sv/MBq). On the other hand, the highest effective dose and the highest effective absorbed dose for 111 In-rituximab by MIRD method is observed in the lung (3.11E-04 Sv/MBq), and the organs that received the next highest doses are kidney, spleen, pancreas and heart with magnitude of 2.26E-04, 1.56E-04, 1.16E-04 and 6.84E-05 Sv/MBq, respectively. Figure 2. shows the comparison of effective absorbed dose by MIRD method and MCNPX simulation code for 111 In - rituximab in human body.

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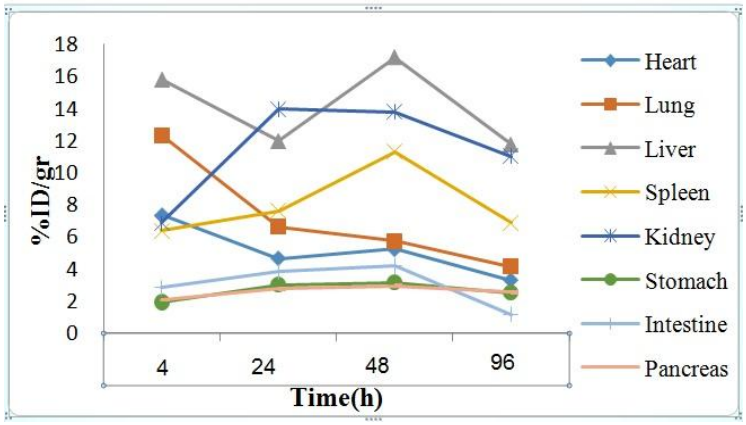

Figure 1. The biological distribution of eight organs of 111 In-rituximab The horizontal axis is displayed as hours post injections (Mean values as the percentage of administered activity per gram (%ID/g))

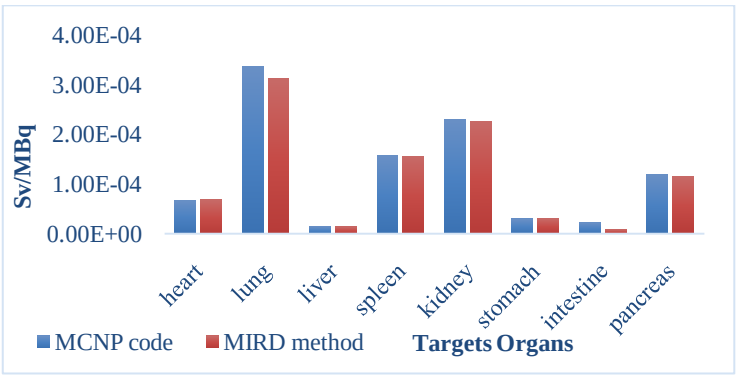

Figure 2. comparison of effective absorbed dose measured by MIRD method and MCNPX simulation code for 111 In - rituximab in human body

4. Discussion

A suitable radiopharmaceutical for therapeutic and diagnostic purposes has several characteristics. One of the most important factors in choosing a radiopharmaceutical in nuclear medicine is the dose delivered to the patient. Indium-111 is one of the most widely used radioisotopes in nuclear medicine. This radioisotope can be used as a radiopharmaceutical by binding to chemical molecules. The motivation for doing this research is to estimate the dose for injection of such radiopharmaceuticals with the aim of radiation protection. 111In-DOTA-rituximab can be used for lymphoma diagnosis and therapy [28]. The uptake of 111In-rituximab in various organs could be due to chemical structure and stability of this radiopharmaceutical.

According to Table 1, the dose delivery to lung measured by MCNPX simulation code and MIRD method is higher than other organs. Although we did not compute the delivered dose to the whole body, according to our results shown in Table 1, effective absorbed dose for all eight organs measured by MIRD method and MCNPX simulation code were close to each other. Many studies have used MCNP and MIRD methods

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together to estimate the internal absorbed dose [29, 30]. In this study, however, the calculation of effective absorbed dose was done using MCNPX simulation code and MIRD method. The advantages of MIRD method are simplicity and efficiency stemming from its use of special absorption fraction and S factor. 111In is a specialized radioisotope because of its gamma ray and beta particle. The gamma ray can penetrate source organs and adjacent organs; nevertheless, beta emission is only localized in source organs because of non-penetrating radiation. In Figure 2, a comparison is shown between MCNPX code and MIRD method. Although there are obvious differences between MCNPX code and MIRD method, the discrepancy is acceptable. The numerical difference between the MIRD and MCNPX simulation codes is due to the lack of consideration of muscle and blood cell tissue and the uniform distribution of radiopharmaceuticals in all organs with the MCNPX code. However, the delivered dose to the target organs has a non-uniform distribution. Yet, an important part of the uncertainty can be due to the conversion of animal data into human data. The difference between the results related to the intestines mostly lies in the difference in geometry of the two methods.

5. Conclusion

In this paper, the equivalent dose and effective dose of 111In-rituximab were estimated in human body. Given that, the delivered doses to different tissues were compared between MCNPX code and MIRD method. The results showed the highest effective doses measured by MIRD method were in lung, kidney, spleen, pancreas, heart, stomach, liver and intestine, in order of quantity; whereas the highest effective doses measured by MCNPX code were in lung, kidney, spleen, pancreas, heart, stomach, intestine and liver. According to the obtained results and comparison between MCNPX simulation code and MIRD method, the numbers are reasonably close to each other, showing that MIRD is an efficient method for dosimetry.

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Conflict of interest

The authors reported no conflict of interest.

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Target organ	Equivalent absorbed dose with MCNPX code (Sv/MBq)	Equivalent absorbed dose With MIRD method (Sv/MBq)	W_T	Effective dose with MCNPX code(Sv/MBq)	Effective dose with MIRD method(Sv/MBq)
Heart	5.61E-04	5.70E-04	0.12	6.73E-05	6.84E-05
Lung	2.80E-03	2.59E-03	0.12	3.36E-04	3.11E-04
Liver	3.83E-04	3.69E-04	0.04	1.53E-05	1.48E-05
Spleen	1.30E-03	1.30E-03	0.12	1.57E-04	1.56E-04
Kidney	1.91E-03	1.88E-03	0.12	2.29E-04	2.26E-04
Stomach	2.50E-04	2.61E-04	0.12	3.00E-05	3.13E-05
Intestine	1.90E-04	7.62E-05	0.12	2.28E-05	9.14E-06
Pancreas	9.91E-04	9.71E-04	0.12	1.19E-04	1.16E-04

Table 1. Estimation of equivalent absorbed dose and effective absorbed dose by MIRD method and MCNPX simulation rituximab in human body-code for 111 In

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