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Orginal Article:
Internal Dosimetry of ^{99m}Tc-Androctonus Crassicauda Scorpion Venom Complex Using MCNPX Simulation Code and MIRD Method for Cancer Study

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Abstract

Introduction: Natural toxins such as scorpion venom have been used to treat different diseases for many decades. Radiolabeled toxins will help the researchers as a cancer diagnostic and therapeutic agent. The biodistribution of radionuclide-venom complex in animal organs and the internal dosimetry estimation are of great importance for the clinical purposes.

Materials and Methods: In this study, the effective dose estimation was performed using MIRD analysis method and MCNPX simulation code. For this purpose, after obtaining the biological distribution results such as %ID/g, accumulation activity of ^{99m}Tc-venom complex, the organs doses were calculated by the two aforementioned methods and human data were extracted from the Sparks-Idogan formula. Stomach, heart wall, kidney, liver, lung, spleen, thyroid, intestine and brain were considered as source organs.

Results: The effective dose of ^{99m}Tc-venom in different organs of the human body was calculated based on the biodistribution in the rat body. The highest and the lowest effective dose delivered to the heart wall (with 3.47E-05 and 4.05E-05 mSv/MBq) and the testic (0.05E-06 and 0.08E-06 mSv/MBq), respectively.

Conclusion: Biodistribution of radiolabeled venom in animal organs indicates that the complex delivers the highest dose to the heart. Also the results of the two dosimetry methods have an acceptable agreement

Keywords: Internal dosimetry, Androctonus crassicauda scorpion venom, ^{99m}Tc, MIRD Method, MCNPX simulation

Introduction

Nowdays, cancer is one of the most important public health problems in many counteries and is one of the two leading causes of death in many regions [1].

The World Health Organization (WHO) foresees that in 2030, more than 21 million new cases of cancer and almost 13.2 million deaths from cancer will occur worldwide each year [2].

Cancer is not a new challenge and has always affected human as evidenced in the fossils of humans thousands

of years ago [3]. The ancients believed that there was no treatment for cancer other than calmative care [4]. For treating cancer, we face many challenges which need to be addressed using novel methods in cancer treatment [5]. Despite the use of several methods in cancer therapy such as surgery, radiotherapy, chemotherapy, etc., these methods are not very desirable and have many side effects such as nausea, vomiting, loss of appetite, weight and hair loss. As a result, researchers are looking for effective treatments to treat cancer with minimal side effects [6].

The incidence of cancer is increasing and finding a treatment method to control it is being done slowly; besides, different side effects of various therapeutic drugs have been observed; therefore, using natural remedies has created a new horizon in the treatment of cancer due to its fewer side effects and availability. In the meantime, many reports and articles have been published about various biological effects especially the anti-cancer effect of animal venom [7].

One of the earliest uses of toxins to treat cancer dates back to the early 20th century. William Coley was a bone surgeon who discovered a combination of heat-killed and systemically administered bacteria which could shrink osteosarcoma [5]. Scorpion venom is one of the most important toxic molecules package that produces pharmacologically active interfering in human body function, but it has great potential as anti-tumor agents [7]. Researches have shown that the scorpion venom has a wide range of medicinal activities, including antibacterial, antifungal and anti-cancer activities. Researchers have also observed the antitumor activity of many scorpion venom in cell lines and animals [8].

Scorpions are arthropods that have adapted to different habitats around the world. There are more than 1,500 species of scorpions worldwide, but less than 25 species are dangerous to humans [9]. Andractonus crassicauda scorpion is one of the most dangerous scorpions in the world and its habitat is arid and tropical areas.

Andractonus crassicauda is a member of the Butide family and has a neurotoxic toxin [10]. Scorpion venom are generally divided into two categories: neurotoxins and cytotoxins. Neurotoxins target the ion channels of K, Ca and Cl in the nervous system, and cytotoxins target the tissues and organs of living organisms [11, 12].

Therefore, according to recent research on antitumor drugs to demonstrate the reduction and elimination of the tumor agent by animal venom, the study of the tissue distribution of the venom labeling with radionuclide is of great importance for clinical diagnostic and therapeutic purposes of cancer.

Several studies have recently been conducted on the issue. For example, Novais et al. [13] studied the tissue distribution of Crotoxin labeled with ^{99m}Tc. Crotoxin or Crtx is the main venom of the Crotalus Durissusterrificus snake. Recent research has proven the antitumor effect of Crtx. The results showed that the main target site of the toxin is in the kidneys [13].

In 2011, Shirmardi et al. [14] studied the synthesis and tissue distribution of 131I-chlorotoxin and its therapeutic use in the treatment of brain tumors. Chlorotoxin is a 36-amino acid peptide, which is found in venom of Leiurus Quinquestriatas. Chlorotoxin can block channels of chloride ions. The toxin binds to glioma cells in brain tumors and provides a new way to diagnose and treat brain tumors.

The results of tissue distribution showed that the concentration and accumulation of toxins were high in the kidneys, liver, intestines and stomach [14].

Shirmardi et al. examined the biodistribution of peptide extracted from the venoms of an Iranian brown snake and a yellow scorpion (ICD-85) labeled with ^{99m}Tc for imaging and treating tumor. The results showed that the liver, kidney and the tumor were the targets of ICD-85 venom [15].

In 2019, Díaz-García et al., investigated the pharmacokinetics and biological distribution of Rhopalurus junciuc scorpion venom labeled with 131I in tumor of mice. The results showed that the presence of 131I-venom in tumor tissue was longer than that of the main organs [16]. ^{99m}Tc is selected as the ideal radiotracer for many experimental studies and nuclear medicine procedures. The ideal properties of ^{99m}Tc are: Half-life of 6 hours, gamma ray energy of 140 keV, ease of access from a generator of 99Mo/^{99m}Tc and well established labeling chemistry [17].

Because researchers have observed the anti-cancer effect of Androctonus crassicauda scorpion venom in vitro experiments [6, 18, 19], the study of the tissue distribution of the radiolabeled venom and the internal dosimetry of the organs is of great importance for the clinical diagnostic and therapeutic purposes of cancer. Therefore, in this study, based on ID / g% data obtained from the biological distribution of ^{99m}Tc-venom complex in the body of mice, we calculated the dose

received by various organs in the human body. Estimation of Organ-Absorbed Doses in Human body was performed using the MIRD and MCNPX simulation codes with the adult male model.

Materials and Methods

Male rats received ^{99m}Tc-venom via a tail and were sacrificed at 15 minutes, 45 minutes and 4 hours after injection and their various organs were dissected, weighted and counted for radioactivity. Data were expressed as the percentage of injected dose per gram of tissue (which was equivalent to the percentage of injected activity per gram %IA/g: %ID/g) as follows (Equation 1) [20, 21].

1. $ID/g\% = \frac{Organ\ Count/Total\ Count}{W} \times 100$

Where Organ Count is the concentration activity on sample tissue, Total Count is the total injected activity to rats, and W is the mass of tissue. The accumulation activity absorbed from the Ãh source in different organs was calculated using Equation 2:

2. $\tilde{A}_h = \int_{t1}^{\infty} A_h(t)dt$

$A_h(t)$ is the accumulation activity of each organ at time (t), and (t) is the time after injecting radiopharmaceutical. Accumulated activity from rat to human body is obtained from the Equation 3 of Sparks and Aydogan [21].

3. $\tilde{A}_{humanorgan} = \tilde{A}_{animalorgan} \times \frac{organmass_{human} / Bodyma}{organmass_{animal} / Bodyma}$

Then, the average absorbed dose was calculated by the MIRD method (Equation 4):

4. $D(r_k) = \Sigma_h \tilde{A}_h s(r_k \leftarrow r_h)$

$D(r_k)$ is the absorbed dose in the target organ (rad or Gy); $\tilde{A}_h$ is the accumulation activity in the source organ and S ($r_k \leftarrow r_h$) is the S-factor which represents the mean absorbed dose to the target organ r_k per unit accumulated activity in the source organ r_h.

S-factor for various radionuclides in doses of medical internal radiation (MIRD.No11) has been published and is available at http://doseinfo-radar/RADARphan.html [20, 21]. S-factor is expressed as follows (Equation 5):

5. $S = (k \Sigma i\ ni\ Ei\ \phi i)/M$

Where ni is the number of radiation with energy E emitted per nuclear transition, Ei is the energy per radiation (MeV); ϕi is the fraction of energy absorbed in the target. M is the mass of target tissue (g or kg) and k is constant factor (rad-g/μCi-hr-MeV or Gy-kg/MBq-sec-MeV).

The average energy per decay for ^{99m}Tc is 0.14 MeV ; the number of particles per decay is n=0.89 and special absorption fraction tables ϕ are available in SAF Adlt from http://doseinfo-radar/RADARphan.html [22, 23]. The effective dose for each tissue was obtained using Equation 6:

6. $E = \sum WT.HT$

, where WT is the tissue weighting factor according to ICRP 106 and HT is the equivalent dose in a tissue or organ [24].

The MCNPX code was used to simulate and calculate dose. In this simulation code, which is based on the Monte Carlo method, the energy range of electron and photon transport is from 1 keV to 100 MeV. Expansion in the low energy range allows for the precise design of photoelectric interactions, the effect of photoelectrons, ogger electrons and specific X-rays.

MCNPX also allows the user to consider a wide range of different conditions. As a result, an independent probabilistic distribution can be defined for the energy, time, place, and direction of the source. In this simulation, the MIRD-ORNL-MALE phantom and Tally *F8 were used to calculate the the absorbed dose for each organ [25].

Results

Table 1 shows the results of the biological distribution of ^{99m}Tc-venom complex (%ID/g) in 15 minutes, 45 minutes and 4 hours after injection. In 15 minutes, the uptake in the liver and kidneys is the highest value. The lungs, spleen, and heart were ranked the third, the fourth, and the fifth, respectively.

The results showed that the concentration of labeled venom in the liver decreased from 2.59% in 15 minutes to 0.92% in 45 minutes after injection, and activity increased in the kidneys from 1.77% in 15 minutes to 1.78% in 45 minutes post injection. This may be due to the hydrophilicity of the complex.

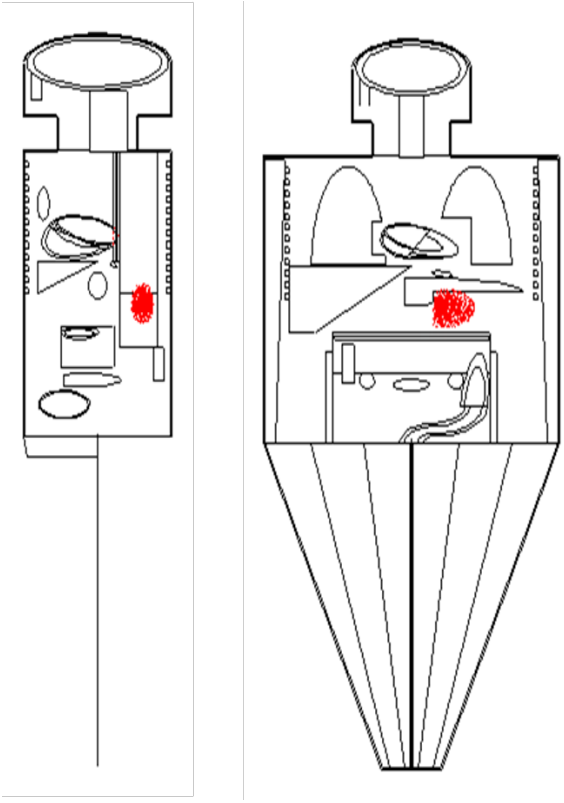

Figure 1. MIRD ORNL- Male phantom [26]

Table 2 shows the simulation results of 1MBq injection of ^{99m}Tc-venom complex using MIRD method and MCNPX code to determine the effective dose in different human organs (lungs, liver, stomach, bladder, testic, brain, colon, thyroid, kidneys, pancreas, spleen, heart wall and small intestine). The highest absorbed dose was seen in heart wall (33.75E-05 and 28.93E-05 mGy/MBq for MIRD and MCNPX respectively). The kidneys, spleen, liver and lungs rank the second, the third, the fourth, and the fifth, respectively. According to the obtained animal data in the heart wall, the effective dose was 4.05E-05 and 3.47E-05 mSv/MBq for MIRD and MCNPX based methods, respectively.

Tissue weighing coefficients for different organs of the body are given in, Table 2 according to ICRP 106, to calculate the effective dose of a radionuclide contributing to the effects of tissue type on dosimetry calculations [27]. Also, the effective doses per gram of different organs of the human body are showen based on rat data at 1MBq activity using both MIRD method and MCNPX simulation. Figures 1 and 2 demonstrated the comparison graphs of the dosimetry using both the MIRD analysis method and the MCNPX simulation.

Discussion

Researchers are becoming more and more knowledgeable about the causes and development of cancer, and they are always looking for newer and better solutions to prevent, diagnose and treat it. Nowadays, new methods are widely used in the diagnosis and treatment of cancer using radiopharmaceuticals.

In order to introduce a new radionuclide for the diagnosis and treatment of various cancers, we need to examine its biological distribution in animal models before clinical use. On the other hand, mistakes in the type and amount of radionuclides increase the risk of secondary cancer. Therefore, estimating the absorbed dose in human body is necessary in order to keep radia-

Table 1. Biodistribution of ^{99m}Tc- venom complex (mean %ID/g)

Organ	%ID/g		
	Mean Value in 15 min	Mean Value in 45 min	Mean Value in 4 h
Blood	1.95	1.10	0.02
Heart	0.71	0.44	0.00
Lung	0.91	0.62	0.02
Stomach	0.22	0.36	0.01
Thyroid	0.35	0.23	0.01
Liver	2.59	0.92	0.04
Intestine	0.33	0.19	0.00
Spleen	0.79	0.51	0.03
Kidney	1.77	1.78	0.11
Brain	0.05	0.04	0.00
Bone	0.39	0.42	0.00

Table 2. The mean absorbed dose and effective dose of different organs of the human body obtained using the MIRD method and the MCNPX simulation code

Organs	Absorbed Dose by MIRD Method (mGy/MBq)	Absorbed Dose by MCNPX Code (mGy/MBq)	Weighting Coefficient (ICRP 106)	Effective Dose by MIRD Method (mSv/MBq)	Effective Dose by MCNPX Code (mSv/MBq)
Lung	12.63E-05	13.14E-05	0.12	1.52E-05	1.58E-05
Liver	12.94E-05	16.00E-05	0.04	0.52E-05	0.64E-05
Stomach	12.32E-05	12.55E-05	0.12	1.48E-05	1.51E-05
Bladder	3.69E-06	4.30E-06	0.04	0.15E-06	0.17E-06
Testic	0.70E-06	0.44E-06	0.12	0.084E-06	0.05E-06
Brain	2.15E-05	2.25E-05	0.01	0.22E-06	0.23E-06
Colon	2.58E-05	2.76E-05	0.12	0.31E-05	0.33E-05
Thyroid	4.24E-05	2.59E-05	0.04	0.17E-05	0.10E-05
Kidneys	26.38E-05	27.95E-05	0.12	3.17E-05	3.35E-05
Pancreas	12.93E-05	15.30E-05	0.12	1.55E-05	1.84E-05
Spleen	25.15E-05	26.67E-05	0.12	3.02E-05	3.20E-05
Heart wall	33.75E-05	28.93E-05	0.12	4.05E-05	3.47E-05
Small intestine	2.96E-05	4.09E-05	0.12	0.36E-05	0.49E-05

tion as low as possible based on biological distribution in animal models [28].

Shen et al. performed radiation dosimetery 131I-chlorotoxin for targeted radiotherapy in glioma mice. Chlorotoxin is a peptide derived from the scorpion venom Leiurus Quinquestriatus, which specifically binds to malignant brain tumors. The results showed that the dose was significant in tumor, stomach, kidneys and brain [29].

In 2009, de Andrade et al. performed 131I-SPGP internal dosimetry in animal model and human extrapolation. SPGP is a polypeptide isolated from the venom of a type of fish called Scorpaena pulmieri and has high anti-tumor activity in malignant tumors; it can be a source of template molecules for the design of anti-tumor drugs. The results showed relatively high doses in organs such as kidneys, bone, muscle, pancreas and bladder for intravenous injection [30].

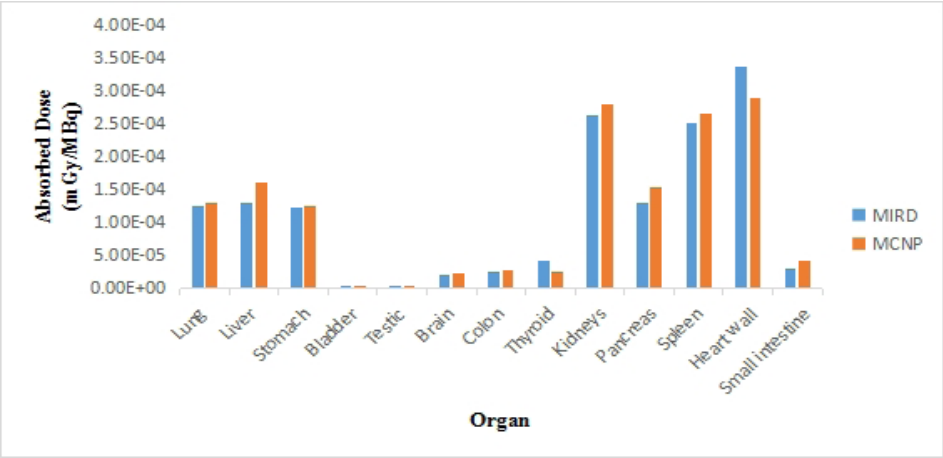

Figure 2. Mean absorbed Dose per gram of different organs of the human body by the two MIRD analysis methods and the MCNPX simulation code

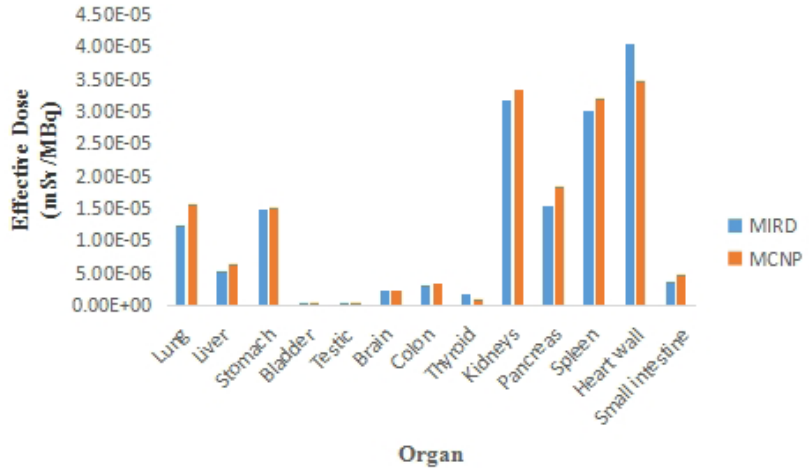

Figure 3. Mean effective dose per gram of different organs of human body by MIRD analysis methods and MCNPX simulation code

In this study, after injection of 1MBq ^{99m}Tc-venom complex, the heart wall absorbed the highest amount of dose with 33.75E-05 and 28.93E-05 mGy/MBq and the lowest dose was in the testic at 0.70E-06 and 0.44E-06 mGy/MBq. The biodistribution results indicated that the concentration of complex in the liver decreased from 2.59% in 15 minutes to 0.92% in 45 minutes after injection, and activity increased in the kidneys from 1.77% in 15 minutes to 1.78% in 45 minutes post injection. This may be due to the hydrophilicity of the complex. The highest and lowest difference between MIRD and MCNPX results are for heart wall and brain, respectively (Figure 3). The difference between MIRD and MCNPX code results may be due to the difference between, measurment methods, human and rat tissues geometry and distribution model of radiopharmaceuticals in tissues (uniformity and non-uniformity of distribution in tissue).

Conclusion

This research presents the internal dosimetry profile of Androctonus crassicauda scorpion venom which is labeled with ^{99m}Tc using direct method. The results show the highest dose in the heart wall, kidneys, spleen, liver and lungs, respectively, after intravenous injection. The results also show that there is an acceptable agreement between the MIRD method and the MCNPX simulation for estimating the absorbed dose. The results of the study will be a step in the future for the clinical diagnostic and therapeutic purposes of cancer using natural products.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Nuclear Science and Technology Research Institute (Code:14000829-162499806).

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Authors' contributions

Conceptualization and Supervision: Seyed Pezhman Shirmardi and Leila Valipour yekani; Methodology: Farshid Babapou and Mostafa Erfanii; Investigation, Writing – original draft, and Writing – review & editing: All authors; Data collection: Leila Valipour Yekany and Abbas Zare Mirakabadi; Data analysis: Leila Valipour Yekany, Mostafa Erfani, and Seyed Pezhman Shirmardi.

Conflict of interest

The authors declared no conflict of interest.

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