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COMPARTMENT BIOKINETIC MODEL FOR ^{90}Y-DOTATOC

Marija Ž. Jeremić[1], Milovan Matović[1,3], Suzana Pantović[3], Dragoslav Nikezić[2], Goran Ristić[4], Dragana Krstić[2*]

[1]Clinical Center Kragujevac, Kragujevac, Serbia
[2]University of Kragujevac, Faculty of Science, Kragujevac, Serbia
[3]University of Kragujevac, Faculty of Medical Science, Kragujevac, Serbia
[4]University of Niš, Faculty of Electronic Engineering, Niš, Serbia

Abstract. *Biokinetic of ^{90}Y-DOTATOC in human body during treatment of neuroendocrine and medullary thyroid tumors is described in this work. For this purpose, the human body may be represented by 4 compartments: blood, kidneys, urinary bladder and tumor. System of differential equations was developed, whose solution is presented in this paper. The aim is the determination of transfer coefficients between individual compartments for a better estimation of the dose in the tumor and other organs of the human body. A computer program is written in standard Fortran90 programming language.*

Key words*: PRRT (Peptide Receptor Radionuclide Therapy), ^{90}Y-DOTATOC therapy, compartment, biokinetic model*

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1. INTRODUCTION

PRRT (Peptide Receptor Radionuclide Therapy) is a molecular targeted radiation therapy, which is based on the intravenous administration of a radioactive single-labeled peptide with high binding affinity for the specific receptors of the tumor, acting on the tumor[1]. ^{90}Y-DOTATOC ([Y-DOTA0, Tyr3] -octreotide) has been successfully utilized during in the past 15 years for the treatment of neuroendocrine tumors that are inoperable, or metastatic, which express the somatostatin receptor type 2 [2,3]. ^{90}Y is a pure β-emitter, whose physical half-life is 64 h. The energy of the released β-particles is up to 2.28 MeV, range of beta particles in soft tissues is short, consequently killing the cells near the point of emission. However, in this type of procedure, a significant amount of ^{90}Y decays in other organs, causing unwanted irradiation of healthy tissue [4,5].

^{90}Y-DOTATOC is slowly administered intravenously, using a pump and the application itself takes 30 minutes. During this time, the radioactive ^{90}Y-DOTATOC is distributed throughout the body, and a fraction is retained in the tumor [6,7]. The experience gained from the implementation of this method is positive, and the final result depends on the individual.

2. MATERIAL AND METHOD

^{90}Y-DOTATOC is used for the PRRT of the patients with neuroendocrine tumors (NETs). A dose in the range of 2.7-5.4 GBq is administered according to standard protocols proposed by European Association of Nuclear Medicine (EANM). In order to protect the renal function, positively charged amino acids are co-administered (lysine and arginine) [8,9]. It is known that this kind of peptide binds very quickly to tumor tissue, while the rest of the activity is excreted through the kidneys and bladder. A certain amount of radioactivity is accumulated in kidneys, which can cause significant damage and reduce kidney functionality. Due to this, there is a tendency to develop personalized dosimetry in order to maximize tumors' doses and minimize kidneys' doses [2].

Measurements were performed on 10 patients who were treated with this therapy in Kragujevac Clinical Centre. Patients were administered with an activity of 90Y-DOTATOC in the range of 2.7-5.4 GBq. Blood samples were taken when the administration was terminated, then every hour in the first 6 hours and after in the intervals of 6 and 12 hours up to 72 hours after administration. Measurements were done with liquid scintillation beta counter RackBeta, LKB Wallac. Urine was also collected and measured in the period of 72 h after application.

In order to better understand the biokinetic of this nuclide in human body, we developed two sets of differential equations which described the behavior of peptides in human body. Human body was considered to consist of four compartments and differential equations describe the balance of ^{90}Y-DOTATOC in each of them. Equations were solved analytically and

* dragana@kg.ac.rs

programmed in Fortran 90. Transfer parameters were varied and the activity in blood was computed and compared with the measured one in order to determine the best set of parameters.

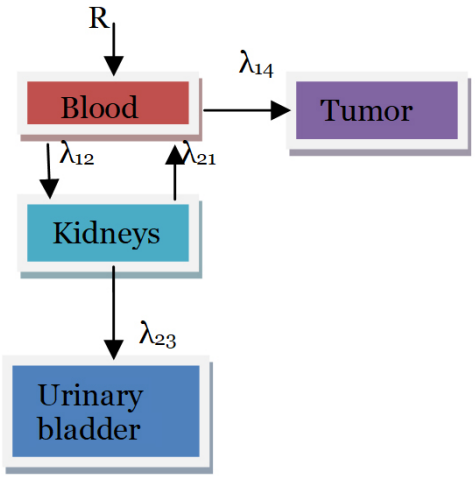

Figure 1. Four compartment model for ^{90}Y-DOTATOC

In the following text, a biokinetic model developed in this work is described. Let A_0 denote the overall activity of ^{90}Y-DOTATOC administered to the patient. The total number of desintegration, U, entered during the application, is the ratio of the activity and constant of radioactive disintegration, λ, $U = A_0 / \lambda$, and the rate of delivery is $R = U / T$, where T is the duration of administration. This activity is transferred from blood to the kidneys, tumor and urinary bladder. The following set of differential equations describes the temporal variation of the number of atoms in the individual compartments during the application of radioactivity.

The temporal variation of the number of atoms in the first compartment, i.e., in the blood, is given by the following differential equation:

blood:

$$\frac{dN_1}{dt} = R - \lambda N_1 - \lambda_{12} N_1 - \lambda_{14} N_1 + \lambda_{21} N_2 \tag{1}$$

The variation the number of atoms in other compartments is shown with the following equations:

kidneys:

$$\frac{dN_2}{dt} = -\lambda N_2 + \lambda_{12} N_1 - \lambda_{21} N_2 - \lambda_{23} N_2 \tag{2}$$

urinary bladder:

$$\frac{dN_3}{dt} = -\lambda N_3 + \lambda_{23} N_2 \tag{3}$$

tumor:

$$\frac{dN_4}{dt} = -\lambda N_4 + \lambda_{14} N_1 \tag{4}$$

where λ_{ij} are transfer rates: λ_{12} from the blood to the kidneys, λ_{21} from the kidneys into the blood, λ_{23} from the kidneys to the urinary bladder, and λ_{14} from blood to the tumor. The above equation presupposes that there is no transfer of tumor back into the blood. N1, N2, N3 and N4 are the number of atoms in the blood, kidney, urinary bladder, and the tumor, respectively.

The previous system is a collection of interconnected linear differential equations that can be solved analytically after a complicated multiple differentiation process and the gradual elimination of certain unknown N_i. The final obtained result is a non-homogeneous differential equation of the second order at N_1:

$$\frac{d^2 N_1}{dt^2} + A\frac{dN_1}{dt} + BN_1 - \lambda_{21} R = 0 \tag{5}$$

where A and B are constants which contain a combination of transfer rates, λ_{ij}.

To solve the previous system of equations, one should use the initial conditions, i.e. at the beginning of application there was no radioactivity in any of the compartments. In mathematical form, this is written as:

$$N_1(0) = N_2(0) = N_3(0) = N_4(0) = 0. \tag{6}$$

In addition, it is necessary to normalize the system, i.e. the sum of activities in all compartments is equal to the applied activity. This condition is written as:

$$N_1(T) + N_2(T) + N_3(T) + N_4(T) = \frac{A_0}{\lambda} \tag{7}$$

The set of equations (1-4) describes the variation of the number of atoms time-period of activity administration. For the period after the end of administration, it is necessary to write a new set of differential equations which differs from the previous one in which $R = 0$. The number of atoms in the compartments in the period after the end of administration of radioactivity is denoted by M1, M2, M3 and M4, to differentiate it from the labels in the first phase.

Initial conditions for the second set of equations are:

$$M_i(0) = N_i(T), \quad i = 1,4 \tag{8}$$

Finally, we get a system of four equations with five unknown parameters λ_{ij}. One independent parameter is needed, and here it is taken from the measurements of radioactivity in blood. Some time t_{exp} after the termination of application, the activity measured in blood was A_{exp}:

$$M_1(t_{exp}) = \frac{A_{exp}}{\lambda} \tag{9}$$

In this study, we developed our own program written in FORTRAN 90 programming language, to solve the system of differential equations and to perform some additional calculations of N_i (t) and M_i (t).

3. RESULTS AND DISCUSSION

As an illustrative example, the results of calculations for one out of 10 patients treated with this method are given.

Figures 1 and 2 show the variations of activity (in GBq) with time (in hours) in blood and urine, respectively, after the termination of the application of radioactivity, estimated by the previously described model (red curve) and measured experimentally (black curve).

Note that there is a good agreement between the measured and estimated values in the blood.

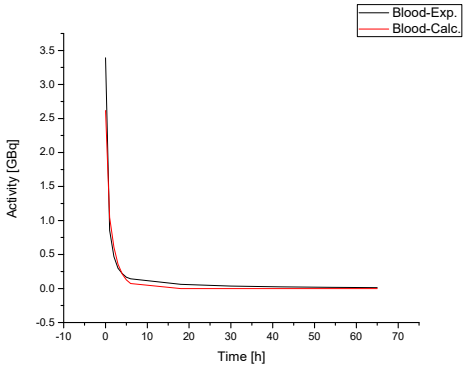

Figure 2. Variation of activity in blood with time-patient 1

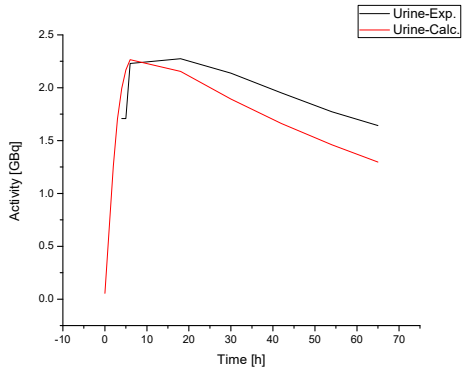

Figure 3. Variation of activity in urine with time- patient 1

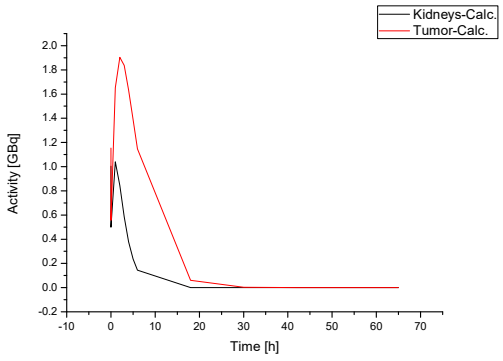

Figure 4. Variation of activity in kidneys and tumor with time – patient 1

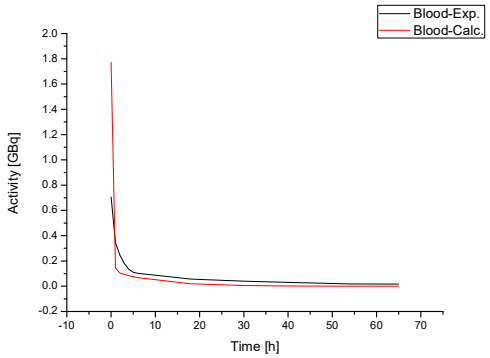

Figure 5. Variation of activity in blood with time- patient 2

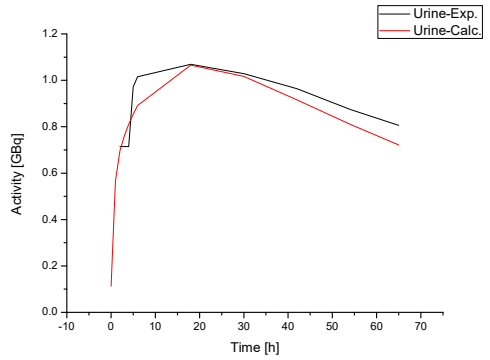

Figure 6. Variation of activity in urine with time- patient 2

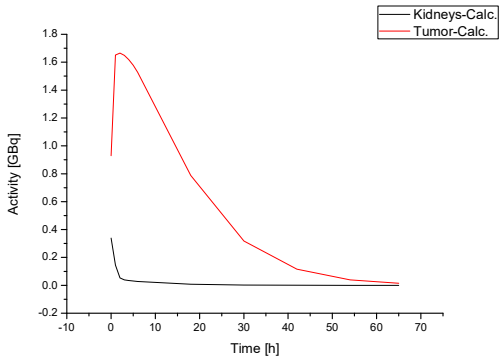

Figure 7. Variation of activity in kidneys and tumor with time – patient 2

In Figure 2, the activity in urine, estimated from the model, follows the trend of measured values, but there is a systematic difference for the time instances following 20 h post administration.

The constants for the transfer rate for one of the patients, based on which the previous graphs are drawn, are:

$$\lambda_{12} = 3,\ \lambda_{21} = 0{,}01,\ \lambda_{23} = 0{,}5,\ \lambda_{14} = 1{,}5 \quad (11)$$

(all in h^{-1}).

From the graphs, an agreement better than 20% between the theoretical model and the experimental

results of activity in blood could be seen. However, in order to obtain a better agreement between the model and the measurements, it is necessary to increase the number of compartments. It is proposed to introduce the fifth compartment, which represents the remainder of the body [10]. This will certainly complicate the solution of differential equations, whose number will increase.

4. Conclusion

This paper presents a model of behavior of ^{90}Y in the human body in DOTATOC-targeted PRRT. The model and the computer program enable the determination of the temporal variation of the number of atoms in the four organs of the human body, which gives the possibility to calculate the absorbed dose in the target tumor and other organs in the body. Depending on the size of the tumor, it is possible to estimate whether the applied activity is sufficient for tumor destruction. It is also possible to estimate the risk of secondary cancers. This will be the subject of our future research.

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References

1. I. Virgolini, T. Traub-Weidinger, C. Decristoforo, "Nuclear medicine in the detection and management of pancreatic islet-cell tumours," *Best Practice & Research Clinical Endocrinology & Metabolism,* vol. 19, no. 2, pp. 213-227, Jun. 2005.
   DOI: 10.1016/j.beem.2004.09.001
   PMid: 15763696
2. A. Otte, R. Hermann, A. Heppeler, M. Behe, E. Jermann, P. Powell, H. R. Maecke, J. Muller, "Yttrium-90. DOTATOC: first clinical results," *Eur. J. Nucl. Medicine*, vol. 26, no. 11, pp. 1439-1447, Oct. 1999.
   DOI: 10.1007/s002590050476
   PMid: 10552085
3. J. J. Zaknun, L. Bodei et al., "The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumors," *Eur. J. Nucl. Med. Mol. Imagin*g, vol. 40, no. 5, pp. 800-816, May 2013.
   DOI: 10.1007/s00259-012-2330-6
   PMid: 23389427
   PMCid: PMC3622744
4. P. Kletting, B. Muller et al., "Differences in predicted and actually absorbed doses in peptide receptor radionuclide therapy," *Med. Phys.*, vol. 39, no. 9, pp. 5708–5717, Sep. 2012.
   DOI: 10.1118/1.4747266
5. J. J. Grudzinski, W. Tome, J. P. Weichert, J. Jeraj, "The biological effectiveness of targeted radionuclide therapy based on a whole-body pharmacokinetic model," *Phys. Med. Biol.*, vol. 55, no. 19, pp. 5723-5734, Oct. 2010.
   DOI: 10.1088/0031-9155/55/19/007
   PMid: 20826898
   PMCid: PMC3835526
6. F. Guerriero, M. E. Ferrari, et al., "Kidney dossimetry in 177Lu and 90Y peptide receptor radionuclide therapy: influence of image timining, Time-activity integration method, and risk factors," *Bio. Med. Research International*, vol. 2013, 2013.
   Retrieved from: https://www.hindawi.com/journals/bmri/2013/935351/
   Retrieved on: Jan. 19, 2017
7. E. J. Rolleman, M. Melis et al., "Kidney protection during peptide receptor radionuclide therapy with somatostatin analogues," *Eur. J. Nucl. Med. Mol. Imaging,* vol. 37, no. 5, pp. 1018–1031, May 2010.
   DOI: 10.1007/s00259-009-1282-y
   PMid: 19915842
8. L. Bodei, M. Kidd et al., "Long-term tolerability of PRRT in 807 patients with neuroendocrine tumors: the value and limitations of clinical factors," *Eur. J. Nucl. Med. Mol. Imaging*, vol. 42, no. 1, pp. 5-19, Jan. 2015.
   DOI: 10.1007/s00259-014-2893-5
   PMid: 25273832
9. M. Matovic, "Peptide receptor radionuclide therapy of neuroendocrine tumors: Case series," *Arch. Oncol.* vol. 20, no. 3-4, pp. 143-148, 2012.
   DOI: 10.2298/AOO1204143M
10. M. Cremonesi, M. Ferrari et al., "Biokinetics and dosimetry in patients administered with ^{111}In-DOTA-Tyr3-Octreotide: Implications for internal radiotherapy with ^{90}Y-DOTATOC," *Eur. J. Nucl. Med.*, vol. 26, no. 8, pp. 877-886, Jul. 1999.
    DOI: 10.1007/s002590050462
    PMid: 10436201