

Estimation of Human Absorbed Dose Using Compartmental Model

M. Mousavi-Daramoroudi, H. Yousefnia, F. Abbasi-Davani, S. Zolghadri

Abstract—Dosimetry is an indispensable and precious factor in patient treatment planning to minimize the absorbed dose in vital tissues. In this study, compartmental model was used in order to estimate the human absorbed dose of ^{177}Lu -DOTATOC from the biodistribution data in wild type rats. For this purpose, ^{177}Lu -DOTATOC was prepared under optimized conditions and its biodistribution was studied in male Syrian rats up to 168 h. Compartmental model was applied to mathematical description of the drug behaviour in tissue at different times. Dosimetric estimation of the complex was performed using radiation absorbed dose assessment resource (RADAR). The biodistribution data showed high accumulation in the adrenal and pancreas as the major expression sites for somatostatin receptor (SSTR). While kidneys as the major route of excretion receive 0.037 mSv/MBq, pancreas and adrenal also obtain 0.039 and 0.028 mSv/MBq. Due to the usage of this method, the points of accumulated activity data were enhanced, and further information of tissues uptake was collected that it will be followed by high (or improved) precision in dosimetric calculations.

Keywords—Compartmental modeling, human absorbed dose, ^{177}Lu -DOTATOC, Syrian rats.

I. INTRODUCTION

NOWADAYS, peptide receptor radionuclide therapy (PRRT) is widely used for the treatment of the abnormalities with SSTR. The best example is SSTR overexpression in neuroendocrine tumors (NETs), which are currently being targeted effectively with SST analogs. Implementation of PRRT in clinical routine was provided a valuable therapeutic tool for patients with advanced tumors [1]. Increased overall survival and improved quality of life for patients with different types of NET are some advantages in PRRT [2].

A series of octreotide analogues have been synthesized and used for somatostatin expressing tumour targeting. Recently, DOTATOC (tetraazacyclododecane tetraacetic acid modified Tyr3-octreotide) was developed for targeting SST receptor-expressing tumors. Clinical investigated with DOTA-TOC have indicated that these radiopeptides are effective both for imaging (i.e., ^{111}In -DOTATOC and ^{68}Ga -DOTATOC) [3], [4] and radionuclide therapy (i.e., ^{90}Y -DOTATOC and ^{177}Lu -DOTATOC) [5], [6].

Among the radionuclides that are used for PRRT, ^{177}Lu

makes it high potential therapeutic option for targeting of the small tumors or metastases owing to its appropriate physical characteristics [$t_{1/2}=6.73$ d, $E_{\beta\text{max}} = 497$ keV, $E_{\gamma}=112$ keV (6.4%), 208 keV (11%)], as well as suitable radionuclide for imaging and post-therapeutic dosimetry [7].

With regard to the importance of minimizing the absorbed dose of vital tissues, dosimetry is a crucial factor in patient treatment planning. Because of the mainly similarities between mouse and human physiology, the radiopharmaceutical biodistribution in a mouse body provided a good indicator of phenomena appearing in human body, and therefore, the behavior study of a new therapeutic agent in the body of a mouse is the first step in examining drug and the medical treatments [8].

Mathematical models which can be used for the prediction of drug behavior in interval times where direct measurements were not performed can play an efficient role in calculating the organ absorbed dose with higher precision [9]. Compartmental model is the most widely used mathematical model which demonstrates the uptake and clearance of the drugs [10].

According to the importance of the internal dosimetry in vital organs during therapy, in the present study, a new approach was assayed for absorbed dose calculation via combination between compartmental model, animal dosimetry and also extrapolated data from animal to human. Owing to the use of compartmental model based on experimental data, it seems that this approach can increase the accuracy of dosimetric calculations. For this purpose, the complex of ^{177}Lu -DOTATOC, as an important therapeutic radiopharmaceutical, was considered. The biodistribution of the complex was assessed up to 168 h after injection, and the pharmacokinetic of the drug was modelled using compartmental model. Finally, the dosimetric data in human organs were estimated by RADAR and the methods of Spark et al. [11].

II. MATERIALS AND METHODS

A. Biodistribution of ^{177}Lu -DOTATOC in Male Syrian Rats

^{177}Lu -DOTATOC was prepared according to the previously reported literature [12]. 3.7 MBq of the complex was injected intravenously into male Syrian rats, while they were sacrificed at selected interval times up to 168 h post-injection. The organs of interest were removed and washed with isotonic saline immediately. The percentage of injected dose per gram for each tissue was determined following the measurement of the mass of each tissue and their activity by a calibrated balance and a p-type HPGe, respectively.

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B. Compartmental Modeling of ¹⁷⁷Lu-DOTATOC

A model is a mathematical description (i.e., one or more equations) of the relationship between tissue concentration and these controlling factors. A full model can predict the time course of radioactivity concentration in a tissue region from knowledge of the local physiological variables and the input function. Each compartment defines one possible state of the tracer, specifically its physical location (for example, intravascular space, extracellular space, intracellular space, and synapse) and its chemical state (i.e., its current metabolic form or its binding state to different tissue elements, such as plasma proteins, receptors, etc.). The compartmental model also describes the possible transformations that can occur to the tracer, allowing it to “move” between compartments [13], [14].

Biodistribution modeling consisted of two steps. At the first stage, a model with only one physical compartment (whole body) and one chemical compartment (¹⁷⁷Lu-DOTATOC) were generated with the compartmental analysis. The values used in this work were residence time from three different kinds of study with free ¹⁷⁷Lu: whole body, average excretion, and maximum excretion as a chemical compartment. Activity concentration values as a time function were prepared after injection of ¹⁷⁷Lu-DOTATOC. Considering the two sources of data in the same modeling, a better consistence was obtained.

The second step was a statistic treatment of biodistribution and dosimetry in rats considering three chemical fractions of the designed radiopharmaceutical: [¹⁷⁷Lu-DOTATOC, free¹⁷⁷Lu, and total radiopharmaceutical (free¹⁷⁷Lu + (¹⁷⁷Lu-DOTATOC) (Fig. 1). These studies were also performed in rats. The selected parameters were very critical, considering the blood flux in each body region and tissue.

C. Dosimetric Calculations

The accumulated activity (\tilde{A}_h) for each animal source organ was calculated with the deployment of (1), where $A_h(t)$ is the activity of each organ at the time t .

$$\tilde{A}_h = \int_{t_1}^{\infty} A_h(t) dt \tag{1}$$

For this purpose, the time-activity curves were obtained by means of the compartmental modelling of the biodistribution data. Subsequently, the accumulated activity calculated for each animal source organ was extrapolated to the equivalent uptake in humans by the proposed method of Sparks and Aydogan [11] as represented in (2).

$$\tilde{A}_{Human\ organ} = \frac{Organ\ mass_{human} / Body\ mass_{human}}{Organ\ mass_{animal} / Body\ mass_{animal}} * \tilde{A}_{Animal\ organ} \tag{2}$$

The absorbed dose in human organs was computed by RADAR formalism based on biodistribution data in the rats [15] and according to the previously reported research. In this research, DFs have been taken from the amount presented in OLINDA/EXM software.

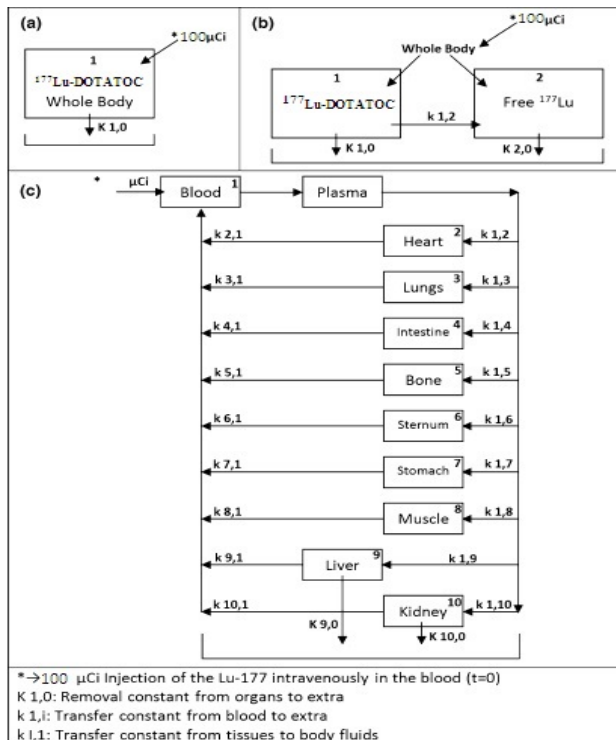


Fig. 1 Selected compartmental analysis models scheme. a) One physical compartment (whole body) and one chemical compartment (¹⁷⁷Lu-DOTATOC). b) One physical compartment (whole body) and two chemical compartments (¹⁷⁷Lu-DOTATOC and free ¹⁷⁷Lu). c) Ten compartment models of a rat

III. RESULTS AND DISCUSSIONS

A. Biodistribution and Compartmental Modelling of ¹⁷⁷Lu-DOTATOC

The radiolabelled complex was prepared with the radiochemical purity of >99%. The compartmental model was used to produce a mathematical description. As a result of modeling, the variation of pharmaceutical concentration in all organs is described with summation of seven or eight exponential terms. The related curves for the main organs have been shown in Fig. 2.

B. Absorbed Dose Calculation

The human absorbed dose of ¹⁷⁷Lu-DOTATOC was estimated based on biodistribution data in male Syrian rats and by means of RADAR method (Table I). As shown in Table I, adrenal and pancreas would receive 0.039 and 0.028 mSv/MBq equivalent absorbed dose values after injection of the complex.

Dosimetric calculations were performed by means of compartmental modelling, a mathematical model for description of the behavior of drugs in the tissues and a flexible approach for prediction of drug concentration time profile. Since biodistribution data were provided with higher precision at the times where no experiment has been performed, this approach can improve the accuracy of the calculations compared with the previously dosimetric

methods.

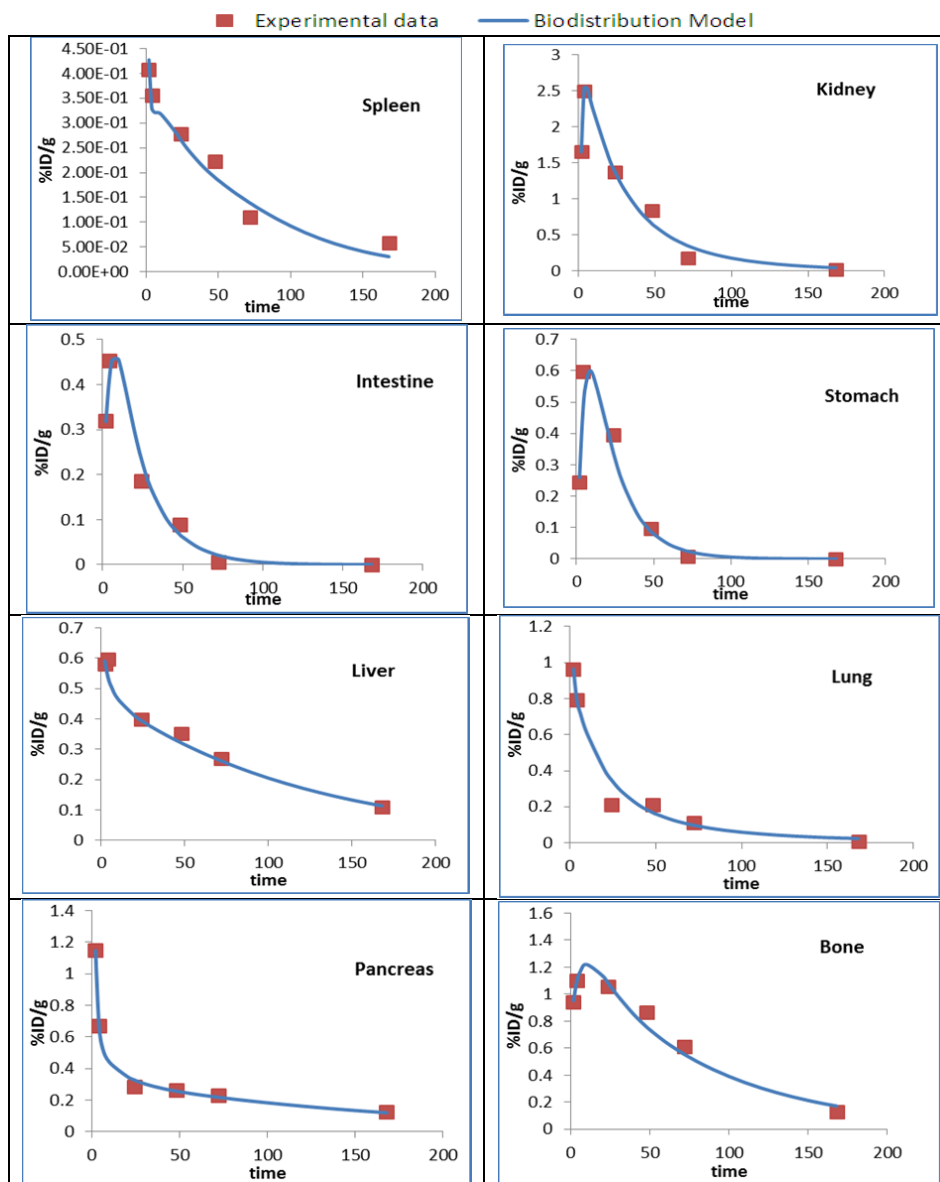


Fig. 2 Temporal behavior of biodistribution of ^{177}Lu -DOTATOC in various organs of wild-type rat.

The results of this study are approximately in accordance with other clinical studies. The absorbed dose of kidneys (as one of the dose limiting organs) was approximately 0.38 mSv/MBq. This value is in comparison with the clinical method of dosimetry used by Guerriero et al. [16] and showed the accuracy of this method for the prediction of absorbed dose values. As indicated in Table I, the radiotracer delivers the safe and appropriate dose for therapy of SSTR-positive tumors.

IV. CONCLUSION

^{177}Lu -DOTATOC was prepared under optimized conditions. In this research, a compartmental analysis was used to obtain the pharmacokinetic model of ^{177}Lu -

DOTATOC. This model can show the behavior of the complex. The pharmacokinetic model can be useful for estimation of the organ absorbed dose with higher precision than the conventional method. The human absorbed dose of ^{177}Lu -DOTATOC was estimated via the compartmental modelling of the extrapolated biodistribution data of rats. One of the purposes of this approach was to obtain the uptake data during those times which no injection was done. Whereas kidneys are the major excretion route and adrenal and pancreas are the SSTR tissues, the highest equivalent absorbed dose values were observed in these organs.

TABLE I
ESTIMATED HUMAN EQUIVALENT ABSORBED DOSE AFTER INJECTION OF
¹⁷⁷Lu-DOTATOC

Target Organs	Equivalent absorbed dose (mSv/MBq)
Adrenal	3.91E-02
Spleen	1.72E-02
Pancreas	2.78E-02
Testes	3.00E-03
Lungs	1.71E-02
Liver	2.80E-02
Kidneys	3.70E-02
Muscle	7.90E-03
Thyroid	1.00E-02
Thymus	3.90E-03
UB Cont	3.90E-03
GB Cont	3.80E-03
LLI Cont	2.56E-02
SI Cont	4.50E-03
Stomach Cont	6.00E-03
ULI Cont	3.90E-03
Heart Cont	6.30E-03
Heart Wall	8.80E-03
Total Body	13.2E-02

GB: Gallbladder Wall; LLI: lower large intestine; SI: small intestine; ULI: upper large intestine; UB: Urinary Bladder Wall.

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