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Time Dependent Biodistribution Modeling of ^{177}Lu-DOTATOC Using Compartmental Analysis

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***Abstract*—**In this study, ^{177}Lu-DOTATOC was prepared under optimized conditions (radiochemical purity: > 99%, radionuclidic purity: > 99%). The percentage of injected dose per gram (%ID/g) was calculated for organs up to 168 h post injection. Compartmental model was applied to mathematical description of the drug behaviour in tissue at different times. The biodistribution data showed the significant excretion of the radioactivity from the kidneys. The adrenal and pancreas, as major expression sites for somatostatin receptor (SSTR), had significant uptake. A pharmacokinetic model of ^{177}Lu-DOTATOC was presented by compartmental analysis which demonstrates the behavior of the complex.

***Keywords*—**Biodistribution, compartmental modeling, ^{177}Lu, octreotide.

I. Introduction

DUE to the increasing of the rates of cancer deaths by 50% in the next 25 years from now [1] and because of the unsuccessful therapy in uncontrollable metastatic cancers, usually new therapeutic methods focused on the treatment of metastasis and inoperable tumors. Targeted radionuclide therapy (TRT) is a new approach for treatment of various abnormalities with SSTR such as neuroendocrine tumors (NETs). Up to now, TRT has shown promising and acceptable results as an attractive potential target for tumor cell-specific therapy and diagnostic imaging [2]-[5].

NETs may arise in many locations; the most common sites are breast, lung, rectum, pancreas, stomach, colon, and duodenum [6] that these tissues are potential targets for peptide receptor radionuclide therapy (PRRT). PRRT in humans has started with the demonstration of SSTR-positive tumors in patients using a radiolabelled somatostatin analogue [7], [8]. A series of octreotide and octreotate analogs were synthesized for therapy of tumor overexpressing SSTR [9] and were labelled with β-emitter radionuclides for therapeutic purposes [10]-[12].

^{177}Lu- octreotide analogue, [DOTA-DPhe1, Tyr3]octreotide (DOTATOC) is currently introduced as one of the suitable options for PRRT [13].

Mathematical models that characterize the behavior of a particular agent may be used to predict its behavior in regions where direct measurements are not possible and these models can be very useful for internal dosimetry calculations when the animal data are not measured [14], [15]. Among different types of pharmacokinetic models, compartmental modeling is the most widely used approach for describing of uptake and clearance drug with high precision [16]-[18]. It simply interpolates the experimental data and allows on empirical formula to determine the activity concentration with time in biodistribution and dosimetry studies [19], [20].

In this study, the authors tried to develop the pharmacokinetic model of ^{177}Lu-DOTATOC from animal data. For this purpose, the biodistribution of the complex was assessed up to 168 h after injection to male-Syrian rats, and the pharmacokinetic of the drug was modelled using compartmental model.

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II. Materials and Methods

A. Preparation and Quality Control of ^{177}Lu-DOTATOC

According to the previous studies [13], ^{177}Lu-DOTATOC was prepared in the optimal conditions. Briefly, 115 μg of the ligand was added to the vial containing 259 MBq of $^{177}LuCl_3$ solution, and the pH was adjusted to 4. The reaction vial was then heated to 95 °C for 30 min.

The radiochemical purity of the complex was checked by the ITLC method. For this purpose, 5 μL of the solution was spotted on Whatman No.3 paper and developed in two solvent systems [A: 10 mmol.L-1 diethylene triamine pentaacetic acid (DTPA) at pH.5 and B: 10% ammonium acetate:methanol (1:1)].

B. Biodistribution and Compartmental Modelling of 177Lu-DOTATOC in Male Syrian Rats

The biodistribution of ^{177}Lu-DOTATOC was carried out at 2, 4, 24, 48, 72 and 168 h post-injection of the complex (3.7 MBq) into male Syrian rats. The organs of interest were removed and washed with isotonic saline immediately. The percentage of injected dose per gram for each tissue was determined according to (1), following by the measurement of the mass of each tissue by a calibrated balance and counting their activity with a p-type HPGe [21]:

$$\%\mathrm{ID/g} = \frac{{}^{\mathrm{A_{Tissue}}}/_{\mathrm{M_{Tissue}}}}{\mathrm{A_{Total}}} * 100 \quad (1)$$

where A_{tissue} is the ^{177}Lu activity in the sample, M_{tissue} is the mass of the sample, and A_{total} is the total activity of ^{177}Lu injected into the rats.

Five rats were considered for each interval time. All values were expressed as mean ± standard deviation (Mean ± SD)

and the data were compared using student T-test. Statistical significance was defined as $P<0.05$.

A compartment is a group of tissues with similar blood flow and drug affinity and each compartment defines one possible state of the tracer, specifically its physical location (for example, intravascular space, extracellular space, intracellular space, synapse) and its chemical state (i.e. plasma proteins, receptors, etc.) [22], [23].

The time-activity curve for each organ was plotted using compartmental model, as the most common approach to pharmacokinetic characterization of drugs, by means of ANACOMPTM software. The formulas of the drugs biological behavior in each organ were obtained.

Biodistribution modelling consisted of two steps: activity concentration values as a time function in measurements of total whole body and activity measurement in samples of blood with projection to total circulating blood volume with ^{177}Lu-DOTATOC. The second step was a statistic treatment of biodistribution and dosimetry in rats.

III. Results and Discussions

A. Preparation and Quality Control of ^{177}Lu-DOTATOC

^{177}Lu was prepared with the specific activity of 2.6-3 GBq.mg^{-1}. The radiolabelled complex was prepared with the radiochemical purity of >99% 21.

B. Biodistribution and Compartmental Modelling of ^{177}Lu-DOTATOC

The percentage of injected dose per gram (%ID/g) for different organs after injection of ^{177}Lu-DOTATOC was calculated by dividing the activity amount of each tissue (A) to the decay-corrected injected activity and the mass of each organ (Table I).

Biodistribution of ^{177}Lu-DOTATOC in male Syrian rats was studied indicating significant uptake in SSTR-positive tissues such as pancreas and adrenals. While rapid clearance was observed after injection of this radiolabeled compound, kidneys recognized as a major excretion route. These findings are in accordance with the other reported literature [13].

The mathematical model uses physiological parameters including organ volumes, blood flow rates, and vascular per abilities; the compartments (organs) are connected anatomically. This allows the use of scale up techniques to predict new complex distribution in humans in each organ. The compartmental model was used to produce a mathematical description of these variations (Table II). Also, the related curves for the main organs have been shown in Fig. 1. In each case, t = 0 corresponds to the time of injection (Fig. 1).

TABLE I
Percentage of Injected Dose per Gram (%ID/g) at 2, 4, 24, 48, 72 and 168 h after Intravenously Injection of ^{177}Lu-DOTATOC into Male Syrian Rats

Organ	2 h	4 h	24 h	48 h	72 h	168 h
Blood	0.90	0.91	0.00	0.00	0.00	0.00
Heart	0.56	0.41	0.06	0.05	0.01	0.00
Kidney	1.65	2.49	1.37	0.83	0.17	0.01
Spleen	0.40	0.35	0.27	0.22	0.11	0.06
stomach	0.24	0.59	0.49	0.09	0.01	0.00
intestine	0.31	0.45	0.18	0.08	0.01	0.00
Lung	0.96	0.79	0.21	0.19	0.11	0.01
Liver	0.57	0.59	0.39	0.35	0.26	0.11
Adrenal	0.00	0.13	0.46	0.57	0.48	0.21
Bladder	0.88	1.01	0.11	0.00	0.00	0.00
Bone	0.94	1.10	1.05	0.86	0.61	0.13
pancreas	1.14	0.66	0.28	0.26	0.23	0.12

TABLE II
The Mathematical Equations of the Drug Biodistribution Derived from the Compartmental Model

1. Spleen

$$f_1 = -1.261e^{-0.1004t} + 0.90e^{-0.96t} - 0.88e^{-0.04t} + (9.8944E-4)e^{-0.001786t} + 0.72e^{-0.0195t} + 0.006531e^{-0.00335t} + 1.6817e^{-0.078t}$$

2. Kidney

$$f_2 = 1.95e^{-0.959t} - 0.65e^{-1.97t} - 0.12e^{-0.91285t} + 0.009e^{-0.537t} + 0.65e^{-0.0199t} + 0.4395e^{-0.019t} + 2.1037e^{-0.0461t} - 9.9e^{-0.9198t}$$

3. Intestine

$$f_3 = -1.529e^{-0.089t} + 0.96e^{-3.74t} - 1.509e^{-0.2214t} + 0.358e^{-0.4923t} + 0.74e^{-0.0488t} + 0.282e^{-0.1099t} + 1.87e^{-0.0987t}$$

4. Stomach

$$f_4 = -1.29e^{-0.105t} + 0.243e^{-6.98t} - 1.5399e^{-0.199t} + (9.9E-5)e^{-0.95t} + 0.75e^{-0.0487t} + (3.64E-4)e^{-0.986t} + 1.99e^{-0.091t}$$

5. Liver

$$f_5 = 0.37e^{-1.7t} + 0.85e^{-3.14t} - 0.0894e^{-0.06t} + 0.14e^{-0.19t} + 0.49e^{-0.007t} - (1.96E-4)e^{-0.01t} + 0.09e^{-0.07t}$$

6. Lung

$$f_6 = 2.03e^{-1.48t} - (9.84E-3)e^{-1.204t} + (2.6E-5)e^{-0.0099t} + 0.1784e^{-0.048t} + 0.28e^{-0.01783t} + 0.01e^{-0.0001t} + 0.475e^{-0.064t}$$

7. Heart

$$f_7 = 1.22e^{-0.472t} + (8.97E-4)e^{-0.0785t} + 0.08875e^{-0.01686t} + (9.979E-7)e^{-0.0009552t} - (9.879E-4)e^{-(9.26E-10)t} - (2.045E-5)e^{-7.08t} - (3.29E-6)e^{-0.189t}$$

8. Blood

$$f_8 = 2.35e^{-1.498t} + 0.9846e^{-0.1076t} + (8.78E-5)e^{(-9.9E-8t)} - (1.372E-3)\,e^{(-0.4531t)} + (7.65E-8)e^{-0.00087t} - 0.001295\,e^{-8.897t} - (5.88E-5)\,e^{-0.0065t}$$

9. Pancreas

$$f_9 = 2.72e^{-0.72t} + 0.235e^{-0.09t} + 0.688e^{-5.6t} - 0.464e^{-0.95t} + 0.046e^{-0.0699t} + 0.00205e^{-0.18t} + 0.339e^{-0.0062t}$$

10.Adrenal

$$f_{10} = -0.53e^{-0.29t} - 0.77e^{-0.06t} - 0.78e^{-0.04t} + 0.0144e^{-0.056t} + 1.094e^{-0.0099t} + 0.0196e^{-(7.01E-6)t} + 0.7e^{-0.081t}$$

11.Bladder

$$f_{11} = 1.01e^{-0.79t} + 0.105e^{-0.105t} + 0.598e^{-1.2t} - 0.84e^{-0.25t} + 0.88e^{-0.112t} + 1.29e^{-0.18t} - 0.06e^{-0.99t}$$

12.Bone

$$f_{12} = -1.24e^{-0.11t} + 0.543e^{-3.9t} - 1.352e^{-0.13t} + 0.089e^{-0.53t} + 0.79e^{-0.0129t} + 0.564e^{-0.015t} + 1.97e^{-0.091t}$$

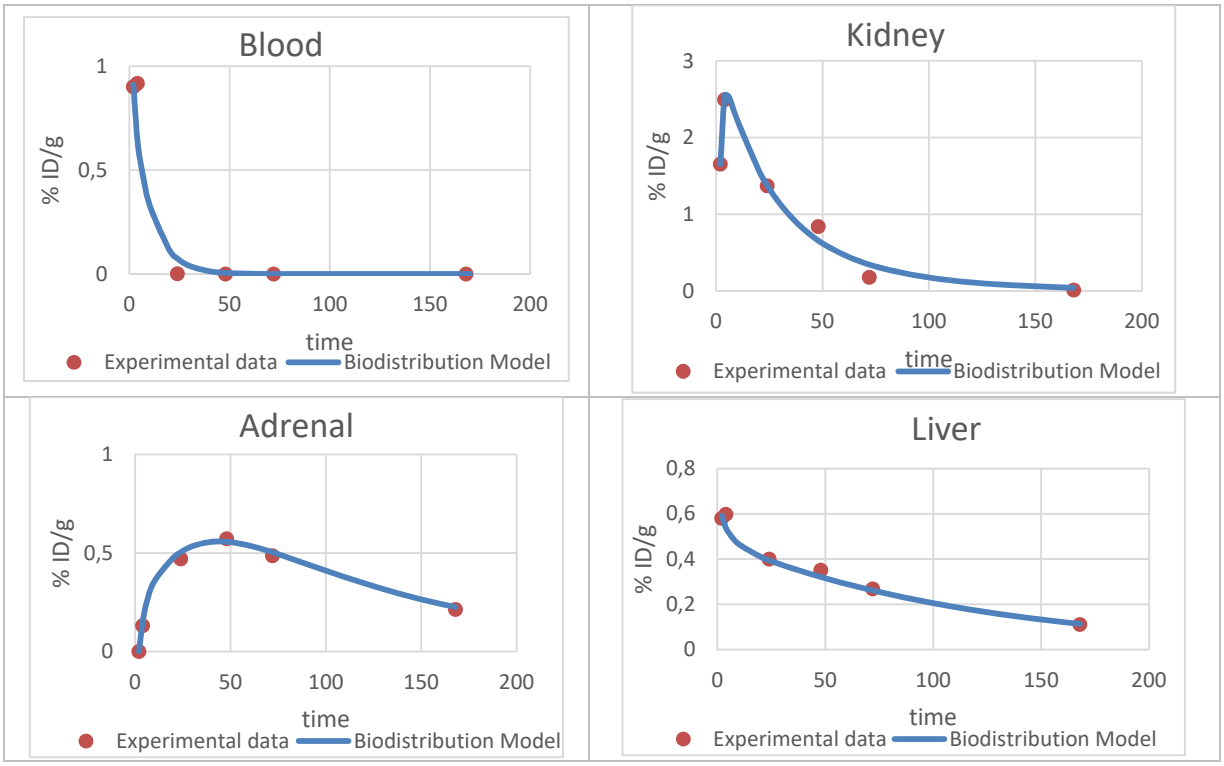

Fig. 1 Temporal behavior of biodistribution of ^{177}Lu-DOTATOC in various organs of rats

IV. Conclusion

^{177}Lu-DOTATOC was prepared under optimized conditions (radiochemical purity: >99% ITLC, >98% HPLC, specific activity of ^{177}Lu: 2.6-3 GBq/mmol). The percentage of injected dose per gram (%ID/g) was calculated for different organs of wild type rats after injection of ^{177}Lu-DOTATOC. A compartmental analysis was used to obtain the pharmacokinetic model of ^{177}Lu-DOTATOC. This model can show the behavior of the complex. One of the purposes of this approach was to obtain the uptake data during those times which no injection was done. The pharmacokinetic model can be useful for estimation of the organ absorbed dose with higher precision than the conventional method.

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