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Compartmental Model for Transportation of ^{177}Lu-DOTATATE into Critical Organs

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Abstract

Neuroendocrine tumors (NETs) are commonly found in the neuroendocrine system and can be recovered by several methods such as surgery, chemotherapy, and radiopharmaceuticals. The latter approach is essential for medical treatment since it becomes the best choice for patients who cannot respond to the first two ways, and it can directly destroy the tumors. However, using radiopharmaceuticals with unsuitable doses may harm some organs like the liver and kidneys. Therefore, this research aims to develop a compartmental model for studying the transportation of ^{177}Lu-DOTATATE into the critical organs and predict the essential parameters for simulation. The model is formed as the system of ordinary differential equations and can be solved by using numerical methods. The results show that the dynamic of concentration of ^{177}Lu-DOTATATE in the selected organs have the same pattern. There is the highest concentration around the first hour after injection, except for liver. Then it started to drop down to zero due to consumption and elimination from the organs. In the future, the model can be used to determine the therapeutic strategy for the improvement of NETs therapy.

Keywords**:** *^{177}Lu-DOTATATE, Compartmental Model.*

1. Introduction

Nowadays, Peptide receptor radionuclide therapy (PRRT) is a specific treatment strategy that uses radiolabeled peptides, which are very important treatment for patients who do not respond to other treatments. The treatment of patients with radiopharmaceuticals will be considered down to the target molecules of the cancer cells in order to determine the appropriate radiopharmaceuticals to bind to the receptors located on the cell walls of the cancer cells, which will be able to treat patients at the right place(Maecke, 2011), (Hussain et al., 2016) and (Ashutosh, 2015).

This research considers the treatment of neuroendocrine tumors (NETs) patients with [^{177}Lu-DOTA0, Tyr3]octreotate (^{177}Lu-DOTATATE) (John, et al., 2013). NETs are rare tumors, which account for only 0.5% of all malignancies. The incidence of NETs is approximately 2 per 100,000, with females who have age under 50 years due to appendiceal location. The main primary sites are the gastrointestinal tract (62–67%) and the lungs (22–27%) (Taal et al., 2004). NETs are developed in the neuroendocrine system, which begins with the specialized cells in the body's neuroendocrine system. These cells have traits of both hormone-producing endocrine cells and nerve cells. They are found throughout the body's organs and help control many of the body's functions. Besides, hormones are chemical substances that are carried through the bloodstream to have a specific effect on the activity of other organs or cells in the body. All NETs are considered as malignant tumors (Schapira, 2019). NETs can begin in any part of the body. The treatment of NETs patients with ^{177}Lu-DOTATATE will be given the right amount because ^{177}Lu-DOTATATE will be transported to the liver and kidneys and if too much accumulation in the liver and kidneys it will be toxic to kidneys and liver.

Overall, this research studies the pharmacokinetic changes of ^{177}Lu-DOTATATE for NETs patients by developing the compartmental model to study the transport of ^{177}Lu-DOTATATE throughout the kidneys, spleen, and the liver. Moreover, we estimate the

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parameters that are useful for simulation. Hence, Mathematical model is another tool to view ^{177}Lu-DOTATATE transportation in the patient's body, and this, combined with additional research, will provide new knowledge that can be used to provide ^{177}Lu-DOTATATE appropriately for NETs patients in the future.

2. Compartmental Model

To form the mathematical model for studying the transportation of ^{177}Lu-DOTATATE into the critical organs, the compartmental model is used for consideration since this technique divides various aspects into separate parts, which are called a compartment (Sandip, 2014) and (Islam et al., 2016).The mathematical model is used to predict the change in the amount of substance that changes with the varying time in each organ and can estimate the amount of substance in every period. In the diagnosis of patients and investigating the amount of substance remaining in the body of the patient, it practically can only be performed with a Single Photon Emission Computed Tomography/ Computed Tomography (SPECT/CT) which cannot be checked at all times since each examination will have a high cost and affecting the patient's body. The researchers then considered creating a model to estimate radiopharmaceuticals and help to see the change over time (Lore et al., 2018).

We set five compartments to form the model. The first part is the ^{177}Lu-DOTATATE that is injected into the patient's body. After that, the substance will move to the other organs in the human's bodies since there are four critical organs in this research (spleen, liver, left and right kidneys) so that we set these organs as another four compartments. To connect the relation of the individual compartment, we review the literature about the behavior of the circulation of ^{177}Lu-DOTATATE in the system.

After the injection, the substance can move to two different paths. The first path is the transportation to the critical organs which have distinct parameters so that four parameters represent the rate of concentration from the source to each organ. The other path is that the substance can decay itself as radioactive properties. Hence the parameter about the substance's half-life should also be considered. For the organs, there is the flow of ^{177}Lu-DOTATATE from the source, which has the same parameters as the mention above, and exceed of substance will transport to plasma again. From this situation, the concentration of ^{177}Lu-DOTATATE in plasma tend to increase. Moreover, there is some elimination in the liver and kidneys. Consequently, these three organs should consider additional parameters that can indicate the rate of eradication without sending to the plasma fluids.

Therefore, we can create the compartmental model as a conceptual diagram, which is shown in Fig 1.

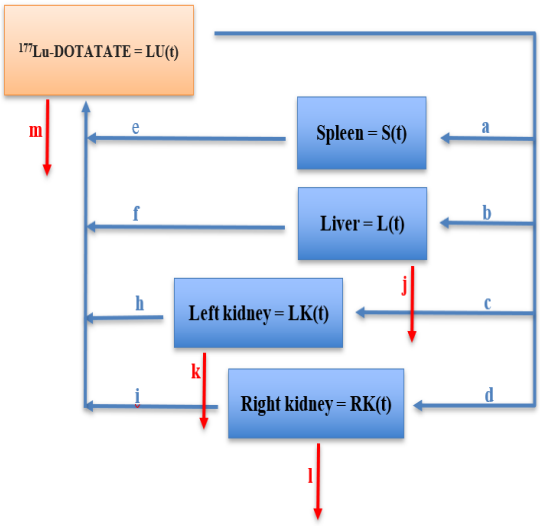

Figure 1: Show the compartmental model of transport of ^{177}Lu-DOTATATE to the spleen, liver, left kidney, and right kidney.

where,

$LU(t)$ is a concentration of ^{177}Lu-DOTATATE,

$S(t)$ is a concentration of ^{177}Lu-DOTATATE in spleen,

$L(t)$ is a concentration of ^{177}Lu-DOTATATE in liver,

$LK(t)$ is a concentration of ^{177}Lu-DOTATATE in left kidney,

$RK(t)$ is a concentration of ^{177}Lu-DOTATATE in right kidney.

and the parameters in this system are,

a is a rate of concentration of ^{177}Lu-DOTATATE from blood to spleen,

b is a rate of concentration of ^{177}Lu-DOTATATE from blood to liver,

c is a rate of concentration of ^{177}Lu-DOTATATE from blood to left kidney,

d is a rate of concentration of ^{177}Lu-DOTATATE from blood to right kidney,

e is a rate of concentration of ^{177}Lu-DOTATATE from spleen to body fluids,

f is a rate of concentration of ^{177}Lu-DOTATATE from liver to body fluids,

h is a rate of concentration of ^{177}Lu-DOTATATE from left kidney to body fluids,

i is a rate of concentration of ^{177}Lu-DOTATATE from right kidney to body fluids,

j is a rate of concentration of removal constant of ^{177}Lu-DOTATATE from liver to extra,

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k is a rate of concentration of removal constant of ^{177}Lu-DOTATATE from left kidney to extra,

l is a rate of concentration of removal constant of ^{177}Lu-DOTATATE from right kidney to extra,

m is a rate of concentration of removal constant of ^{177}Lu-DOTATATE to extra.

3. The mathematical model

After we have the compartmental model, we can form the mathematical model of the transportation of ^{177}Lu-DOTATATE in human bodies. Then each compartment can be considered the rate of change of the concentration of the substance. Hence, we obtained the model which is formed in the system of ordinary differential equations, as shown below:

$$\frac{dLU(t)}{dt} = eS(t) + fL(t) + hLK(t) + iRK(t) - aLU(t) - bLU(t) - cLU(t) - dLU(t) - mLU(t) \quad (1)$$

$$\frac{dS(t)}{dt} = aLU(t) - eS(t) \quad (2)$$

$$\frac{dL(t)}{dt} = bLU(t) - fL(t) - jL(t) \quad (3)$$

$$\frac{dLK(t)}{dt} = cLU(t) - hLK(t) - kLK(t) \quad (4)$$

$$\frac{dRK(t)}{dt} = dLU(t) - iRK(t) - lRK(t) \quad (5)$$

The equation (1) from the system shows the transportation of ^{177}Lu-DOTATATE concentration by plasma to the spleen, liver, left and right kidneys with the rates of concentration $a, b, c,$ and $d,$ respectively. In addition, there is the transportation of ^{177}Lu-DOTATATE from the organs to body fluids with the rate e, f, h and $i,$ respectively, while m is the rate of removal of ^{177}Lu-DOTATATE to extra. Equation (2) shows the transportation of ^{177}Lu-DOTATATE concentration by plasma to spleen with the rate a and the removal from spleen to body fluids with the rate e.The transportation of ^{177}Lu-DOTATATE concentration by plasma to the liver can be shown by the equation (3) with rate b and the removal from the liver to body fluids with rate f, while j is the rate of the elimination of ^{177}Lu-DOTATATE by liver. Next, the equation (4) shows the transportation of ^{177}Lu-DOTATATE concentration by plasma to left kidney with rate c and the removal from left kidney to body fluids with rate h, while k is the rate of the elimination of ^{177}Lu-DOTATATE by left kidney. Finally, the equation (5) shows the transportation of ^{177}Lu-DOTATATE concentration by plasma to right kidney with rate d and the removal from right kidney to body fluids with rate i, while l is the rate of the elimination of ^{177}Lu-DOTATATE by right kidney.

Since the data collected from patients cannot be received at all times, then we use mathematical models to predict the radiopharmaceuticals changes by using the systems of equationsas show above. After that we fit the parameters in the systemsto find most suitable value which related the real data.

4. Results

After the development of the system of ordinary differential equations, we used classical Runge-Kutta method (RK4) to simulate the system for finding the parameters which have suitable fit with the observed data from the real measurement of the concentration of ^{177}Lu-DOTATATE from patients in five different time (0, 0.5, 4, 24 and 124 hours) which is shown in Table 1(Dale et al, 2018).

Table 1: The observed data of neuroendocrine patient from Dale et al., 2018.

Observed data	Value				Unit
	0.5 hr	4 hr	24 hr	124 hr	
$S(t)$	350.55	257.683	229.017	111.803	Bq/ml
$L(t)$	385.118	396.351	386.578	185.837	Bq/ml
$LK(t)$	1111.902	609.546	414.749	118.672	Bq/ml
$RK(t)$	1335.111	671.405	438.261	114.888	Bq/ml

Then we put this data as an input in the R program to simulate and fitting the parameters in the developed model. For the initial data, we assume the situation that the doctor injects the substance directly to the patients, while the patients never have any radiopharmaceuticals before so that there is no ^{177}Lu-DOTATATE in the bodies. Therefore, the initial data can be shown in Table 2.

Table 2: The initial data for the simulation and fitting parameters.

Initial data	Value	Unit
$LU(t)$	7.4	GBq
$S(t)$	0	GBq
$L(t)$	0	GBq
$LK(t)$	0	GBq
$RK(t)$	0	GBq

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However, the referred data of the concentration of ^{177}Lu-DOTATATE is specific for the observed patients so that we need to transform the unit to Bq/mL by dividing the volume of blood in the adult human. This is because the adults are the main group of population who have the most risk for finding NETs. So, the initial concentration of substance that we use in the simulation is 1,298,245 Bq/mL.After that, we have the results of parameters which is fitted by the program and the numerical results that they are shown the dynamic of ^{177}Lu-DOTATATE in the critical organs. Both of then are shown in Table 3 and Fig 2, respectively.

Table 3: The value of parameters from the fitting process.

Parameters	Value	Unit
a	0.0003	hr^{-1}
b	0.00007	hr^{-1}
c	0.025	hr^{-1}
d	0.006	hr^{-1}
e	0.8	hr^{-1}
f	0.1	hr^{-1}
h	2	hr^{-1}
i	2	hr^{-1}
j	0.01	hr^{-1}
k	30	hr^{-1}
l	4	hr^{-1}
m	0.005	hr^{-1}

The result show that the dynamics of ^{177}Lu-DOTATATE concentration in the left and right kidneys, which are shown by blue and black lines, have a sharp increase in the first half an hour and reach the peak around 1,200 Bq/mL and 1,000 Bq/mL. Then, it starts to decrease until the end of the simulation continuously.

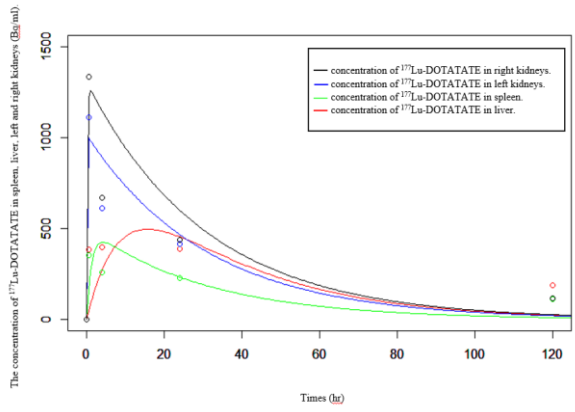

Figure 2: The dynamics of ^{177}Lu-DOTATATE concentration in spleen, liver, left, and right kidneys.

At the same time, the green line shows the dynamics of ^{177}Lu-DOTATATE concentration in the spleen. It can be seen that the concentration of the pharmaceutical increases rapidly, but it is not as high as both kidneys, approximated by 500 Bq/mL. Then the concentration slightly drops and tends to stable when it falls down to around 0 Bq/mL.

Finally, the red line shows the dynamics of ^{177}Lu-DOTATATE concentration in the liver, and it is obvious that the organ increases with the lower rate compare to the others, which spend around ten hours to reach the peak. After that, the concentration slightly decreases and approaches to nearly zero.

Overall, the patterns of ^{177}Lu-DOTATATE transportation in the three organs are nearly similar. With its move to the organs with high concentration and reach the highest points, which depends on each target. Then the concentrations slightly drop and stabilize at zero, which means the substance is spent to destroy cancer cells and eliminate by each organ.

5. Discussion

From the simulation of the compartmental model for the critical organs which can be found the toxicity from the exceed of ^{177}Lu-DOTATATE, If we can determine the initial concentration of the substance with appropriate dose for specific patients, it will increase the performance of medical treatment and decrease rate of toxicity in the organs. For example, the interval of time from starting point to the first half an hour, it is the maximum value of the absorption rate in kidneys so that doctors can consider giving ^{177}Lu-DOTATATE continuously to patients without the occurring of toxics.

Hereafter, this model can be developed to have more suitable for the transportation of ^{177}Lu-DOTATATE in complete circulation in human's bodies. This will support the medical treatment to have more efficiency.

6. Conclusion

This research develops the compartmental model for the transportation of ^{177}Lu-DOTATATE concentration to the main important organs, which can be used to study the toxicity of exceed absorption. The selected organs are spleen, liver, left, and right kidneys. The model is developed by considering the concentration that flows from the source of injection and carry by plasma to the organs. Furthermore, the rate of removal of the substance due to consumption for treatment purposes and elimination in each target are also considered. Hence, we have the model formed in the system of ordinary differential equations. The concentration simulation is calculated by using numerical methods, which are shown the movement of ^{177}Lu-DOTATATE in the studied organs.

The results obviously show that all organs have nearly the same trends of dynamic concentration of ^{177}Lu-DOTATATE. There is a high concentration at first, then reaching the highest point at the early period of the simulation around an hour, except for the liver that has

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the most delay of absorption, taking around 10 hours. After that, the concentration of substance is reduced in all organs due to consumption for treatment and elimination.

Therefore, this model can be used to determine the concentration of ^{177}Lu-DOTATATE in different intervals of time in some important organs, so that we can also use the model as a tool to calculate the amount of ^{177}Lu-DOTATATE for specific patients and predict the concentration for after injection in the organs. As a result, doctors can plan a suitable treatment for the improvement and accuracy of medicine.

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References

[1] Ashutosh Dash, Sudipa Chakraborty, Maroor Raghavan Ambikalmajan Pillai, and Furn F. (Russ) Knapp Jr. (2015).Peptide Receptor Radionuclide Therapy :An Overview, *Cancer Biotherapy and Radiopharmaceuticals*, 30,2.

[2] Dale, L.B., Kathy, P.W. and Paul, J.R., et al. (2018). Evaluation of absorbed dose using sequential quantitative SPECT/CT following ^{177}Lu -DOTATATE metastatic neuroendocrine tumor therapy. *Siemens Medical Solutions USA*.

[3] Islam, R., Ghani, A.B.A., Kusuma, B., Theseira, B.B. (2016). Education And Human Capital Effect On Malaysian Economic Growth. International Journal of Economics and Financial Issues, 6 (4), pp. 1722-1728.

[4] Hussain, A., Mkpojiogu, E.O.C., Kamal, F.M. (2016). Mobile Video Streaming Applications: A Systematic Review Of Test Metrics In Usability Evaluation. Journal of Telecommunication, Electronic and Computer Engineering, 8 (10), pp. 35-39.

[5] John, J., Zaknun, L., Bode, J., Mueller-Brand, M. E., Pavel, R. P., Baum, D., Hörsch, M. S., O'Dorisio, T. M., O'Dorisiol, J. R., Howe, M., Cremonesi, D. J., and Kwekkeboom.(2013), The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT)in neuroendocrine tumours, *Eur J Nucl Med Mol Imaging*, 40, 800–816.

[6] Lore Santoro, Erick Mora-Ramirez, Dorian Trauchessec, Soufiane Chouaf, Pierre Eustache, Jean-Pierre Pouget, Pierre-Olivier Kotzki, Manuel Bardiès and Emmanuel Deshayes. (2018), Implementation of patient dosimetry in theclinical practice after targeted radiotherapy using [^{177}Lu-[DOTA0, Tyr3]-octreotate. *European Journal of Nuclear Medicine and Molecular Imaging.* 8,103.

[7] Maecke. H.R. and Reubi, J.C. (2011), Somatostatin receptors as targets for nuclear medicine imaging and radionuclide treatment. *J Nucl Med*, 52, 841–844.

[8] Sandip Banerjee. (2014*), Mathematical Modeling*, A Chapman and hall book, London New York.

[9] Schapira, L., Neuroendocrine Tumor of the Lung: Introduction, *Cancer.Net* [Online], Available: https://www.cancer.NETs/cancer-types/neuroendocrine-tumor-lung/introduce-tion [2019, November 26].

[10] Taal, B.G. and Visser, O. (2004), Epidemiology of neuroendocrine tumors, *Neuroendocrinology*, 80, 3–7.