KINETICS MODEL FOR LUTATE DOSIMETRY

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ABSTRACT

The use of compartimental analysis to predict the behavior of drugs in the organism is considered the better option among numerous methods employed in pharmacodynamics. A six compartments model was developed to determinate the kinetic constants of 177Lu-DOTATATO biodistridution using data from one published study with 67 patients treated by PRRT (Peptide receptor radionuclide therapy) and followed by CT during 68,25 hours. The compartmental analysis was made using with the software AnaComp®. The influence of the time pos-injection over the dose assessment was studied taking into account the renal excretion management by aminoacid coinfusion, whose direct effects persist in the first day. The biodistribution curve was split in five sectors: 0-0.25h; 0-3.25h; 3.25-24.25h; 24.25-68.25h and 3.25-68.25h. After the examination of that influence, the study was concentrated in separate the biodistribution curve in two phases. Phase 1: governed by uptake from the blood, considering the time pos-injection until 3.25h and Phase 2: governed by the renal excretion, considering the time pos-injection from 3.25h to 68.25h.The model considered the organs and tissues superposition in the CT image acquisition by sampling parameters as the contribution of the activity concentration in blood and the relation between the sizes of the whole body and the measured organs. The kinetic constants obtained from each phase (1 and 2) were used in dose assessment to patients in 26 organs and tissues described by MIRD. Dosimetry results were in agreement with the available results from literature, restrict to whole body, kidneys, bone marrow, spleen and liver. The advantage of the proposed model is the compartimental method quickness and power to estimate dose in organs and tissues, including tumor that, in the most part, were not discriminate by voxels or phantoms built using CT images.

Key words: LUTATE, Compartimental analysis, Biodistribution, Patient dosimetry.

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1. INTRODUCTION

Neuroendocrine tumors (NETs) are rare malign diseases whose detection all most part of the times is too late for the chirurgical removal. In these cases, the use of labeled peptides, analogous of natural hormones may be used to reduce symptoms and improve patients' welfare by peptide receptor therapy (PRRT)[1,2,3,4,6].

LUTATE is a somatostatina analogous binding with the somatostatina receptors 2 and 5 (SRRT2 and SRRT5) and has been considered the best radiopharmaceutical for neuroendocrine tumors PRRT[2,3,5]. However, its high SRRT1 and SRRT2 affinity drops levels of ^{177}Lu into glomeruli kidneys letting radiation dose able to start early and later tissues reaction as described in the Publication 118 of the International Commission on Radiological Protection (ICRP 118)[7]. Consequently, PRRT with somatostatina analogous has in the patient dosimetry the success key.

Traditional techniques to patient dose assessment have been using Mont Carlo or kinetic methods based in direct integration using trapezoidal or least square analysis.

Compartmental analysis is able to describe all phenomena by equations and curves as to predict the behavior of drugs in the organism and it has been considered the better option among numerous methods employed in pharmacodynamics.

Using this principle, calculated fractional transfer coefficients (*k*) of LUTATE biodistribution may be useful to estimate dose in many organs and tissues. The goal of this method is the ability to separate overlapping contributions by mathematical resources as the sampling condition. Though, discriminating the blood contribution over the dose in measured organ's *ROI* as well discriminating tumor and normal tissues overlapping.

2. EXPERIMENTAL

2.1. Human data source

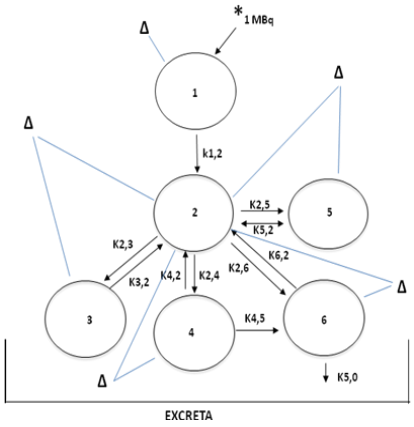
The source of Human data with LUTATE concentration expressed as fraction of initial administrated activity as a time function, %IA(t) were obtained from Wehrmann et al.[5] published studies assessing PRRT (Peptide receptor radiotherapy) patients. Where the organs and tissues %IA(t) described were: whole body, blood, spleen, kidney and rest of the body.

As these data include the tumoral lesions uptakes, these values were subtracted, and the organs and tissues concentration normalized to 100% to allow them comparable with the biodistribution studies in animals.

2.2. Compartmental analysis applied to LUTATE biodistribution

The six compartment model used to calculate *fractional* transfer coefficients (k) that correspond to blood→organs and organs→blood and kidney→excretion of the LUTATE, is presented in the Figure 2. This is the base for the AnaComp feeding.

As the original patients' data include the tumoral lesions uptakes, these values were subtracted, and the organs and tissues concentration normalized to 100% to allow them comparable with the biodistribution studies in animals.



(∗) Initial Injected Activity.

Compartments:
(1) infusion pump, (2) whole body, (3) spleen, (4) kidneys, (5)rest of the body and (6) urinary bladder.

(Δ) Sigma Sampling Parameters *si,j*.
Where *i* is the data series name and *j* is the compartment name:
s1,1; s2,2; s2,3; s2,4; s2,5; s3,2; s4,2; s4,4; s5,2; s5,5.

$k_{j,i}$ Fractional transfer coefficients from the compartments *j* (exit) to *i* (enter).

Figure 1. Scheme of compartmental analysis representing the model applied using PRRT Patient data.

Interrupt request

The LUTATE biodistribution studies were split in five sectors (Phases from 1 to 5), using a procedure called ***interrupt request*** to study the Dose response as a function of the elapsed time between the measures. The considered times were: 0 to 0.25h; 0 to 3.25h; 3.25 to 24.25h; 24.25 to 68.25h and 3.25 to 68.25h.

After the examination of that influence, the study was concentrated in separate the biodistribution curve in only two phases to estimate the LUTATE biological half-life. Phase 1: governed by the uptake from the blood, considering the time post-injection from 0 to 3.25h and Phase 2: governed by the renal excretion, considering the time post-injection from 3.25h to 68.25h.

Feeding AnaComp® with data *ROI* and the sampling tool Sigma parameter (s)

The Sigma (***s***) parameter is a tool to study the interference of the tissues overlapping in the ROI analysis. Human anatomical data from ICRP 89[8] was used as sampling parameters to the blood residue in the organs and tissues. Overlapping ratios between the organs and whole body as based in calculated ratios considering organs mass and body mass. The sampling parameters to the model are shown in the Table 1.

2.3. Dose calculating

The kinetic constants obtained from each phase (1 and 2) were used in dose assessment to patients in 26 organs and tissues described by MIRD as described previously[9]. The dose calculating was made using the male adult phantom (70kg), corresponding to Reference Man (ICRP 103)[10] and computing all interactions due gamma and beta radiations of the ^{177}Lu.

Dose was expressed in dose coefficients as recommended to radiopharmaceuticals (ICRP 106)[11].

Table 1. Sampling description (Sigma parameter - *s*) considered in the compartmental analysis from Wehrmann et al. patients' data.

Sample(Δ) Description	COMP	(FCOMP)	(BL%/ORG)	(MORG/MWB)	Sigma (*s*) Values
Coinfusion pump	**1**	**1**	**0**	**0**	**1**
Blood	**2**	**1**	**0**	**0**	**1**
Blood in the spleen	**2**	**0**	**0.014**	**0**	**0.014**
Spleen	**3**	**1**	**0**	**0**	**1**
Rest of the body	**5**	**0**	**0**	**0.00011+0.00214**	**0.225**
Blood in the kidneys	**2**	**0**	**0.0124**	**0**	**0.0124**
Kidneys	**4**	**1**	**0**	**0**	**1**
Rest of the body over kidneys	**5**	**1**	**0**	**0.0077+0.0004430**	**0.0123**
Blood over rest of the body	**2**	**0**	**0.075**	**0**	**0.075**
Rest of the body	**5**	**1**	**0**	**0**	**1**
Blood over in the rest of the body	**2**	**0**	**0.0002**	**0**	**0.0002**
Rest of the body over the bladder5	**5**	**1**	**0**	**0.00015+0.0007**	**0.00023**
Bladder	**6**	**1**	**0**	**0**	**1**

COMP: 1 blood, 2 spleen, 3 kidneys, 4 rest of the body and 5 bladder) Compartments considered in the study. (FCOMP) Sample fraction in the same compartment. (BL%/0RG) Blood concentration in the organs as % of the total volume. (MORG/MWB) Ratio between organs and whole body average mass (ICRP89)[8] in addition to average blood concentration in the adjacent overleapt tissues contributing to ROI - proportionally to these ratios.

3. RESULTS AND DISCUSSION

The Figure 2 is a biodistribution graphics draw up using the original Wehrmann et al.[5] data normalized to wealthy humans conditions.

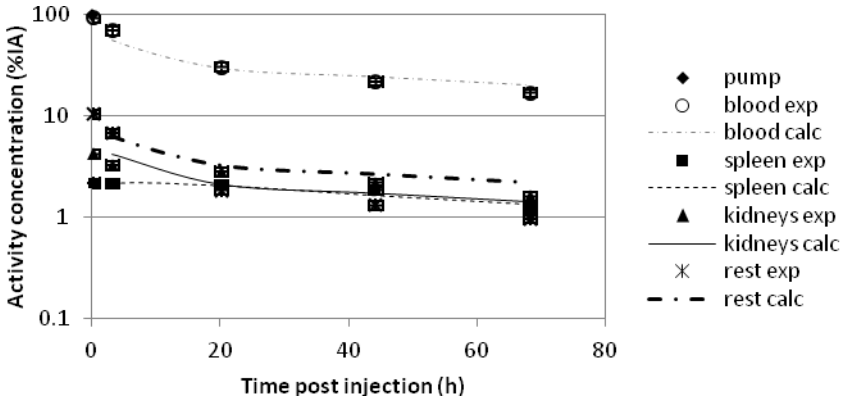


Figure 2. Normalized LUTATE biodistribution curves obtained to wealthy humans conditions.

Fractional transfer coefficients calculated to phases 1 and 2 are given in Table 2. As expected, the first parts of the kinetic curves are faster.

Table 2. Fractional transfer coefficients (*k*) of LUTATE biodistribution in Adult Human.

Fractional transfer coefficients (*ki,j*) (hours^{-1})	**time=0-3.25h p.i. (Phase 1)**	**time=3.25-68.25h p.i. (Phase 2)**
k5,0 (from bladder to excretion)	1.43E+00	4.15E-02
k2,1 (from spleen to blood)	4.00E+02	4.44E-02
k3,1 (from kidneys to blood)	1.25E-02	9.99E-03
k4,1 (from rest of the body to blood)	8.36E-02	2.11E+01
k5,1 (da bexiga para o sangue)	4.87E+00	1.00E-06
k1,2 (from blood to spleen)	6.00E-06	2.86E-03
k1,3 (from blood to kidneys)	1.25E-02	1.13E-02
k1,4 (from blood to rest of the body)	2.13E-01	2.00E-06
k1,5(from blood to bladder)	1.87E-01	0.00E+00
k3,5 (from kidneys to bladder)	2.00E-06	1.23E-01

(p.i.) Time post injection.

Using fractional transfer coefficients (*k*), the absorbed dose in the organs and whole body due to LUTATE biodistribution are presented in the Table 3 in comparison with original Wehrmann et al.[5] data.

Dosimetry results were in agreement with the available results from Wehrmann et al.[5], restrict to whole body (0.045mGy/MBq), kidneys (0.801mGy/MBq), spleen (1.81mGy/MBq). In the liver, the lowest dose would represent a best discrimination between tumoral lesions and normal tissue (0.0368mGy/MBq).

Results provide evidence that absorbed doses are higher in the period between t=3.25h and t=20.25h, range in which the cocktail of aminoacids has supposedly all excreted, but in which there is still a considerable concentration of activity in the patient's body.

In the absence of data relating to the period between t=3.25h and t=20.12h it became impossible to evaluate the contribution of dose in the kidneys and bladder in this range of time pos-injection. As a consequence, the Phase 2 between t=3.25h and t=68.12h seems to represent a normalization process results of all the biodistribution.

The absorbed dose values calculated using compartmental analysis developed in this work have agreement with the results obtained by other authors mainly considering the Phase 2 of the biodistribution.

This may denote that in the Wehrmann et al.[5] original study the contribution of post injection period of the radiopharmaceutical between t= 0.25h and t=3.25h was not properly considered. As there were not intermediate measures in this time interval, the integrated area under the curve of biodistribution based in non-compartmental models assumes the trapezoidal shape being unable to reproduce the kinetic phenomena that occur during this period. For that reason, it would be important to introduce intermediate measuring times in intervals between t=0.25h and t=3.25h and between t = 3.25h and t = 20.25h., p.i..

Another question would be the initial concentration of radioactive tracer in the central compartment of distribution (pool) considered by Wehrmann et al.[5]. In the present model, the t=0 is the time when it started the LUTATE induction pump. So, that time is considered the time of blood circulation and radiopeptide and the fast uptake by the organs. Never, in the time of the biodistribution study, the concentration in the compartment of distribution could be considered as 100% by the injected activity.

Table 4. Comparison of LUTATE dosimetry results between Human adult (70kg), based in Wehrmann et al.[5]							
Biodistribution Phase	**This work[a]**						**Wehrmann et al.[b]**
	Time post injection (hours)				**Average Absorbed Dose†**	**Average Absorbed Dose‡**	
	0-3.25	3,25-20,25	20,25-68,25	3.25-68.25			
Organ/tissue	**Absorded Dose mGy/MBq**						
Adrenals	0.008	0.165	0.051	0.069	0.077	0.077	
Brain	0.006	0.151	0.046	0.062	0.068	0.068	
Breast	0.006	0.149	0.045	0.061	0.067	0.067	
Biliary vesicle	0.007	0.161	0.049	0.067	0.074	0.074	
Large Int. Inf	0.007	0.162	0.051	0.074	0.081	0.077	
Small intestine	0.007	0.161	0.05	0.069	0.038	0.038	
Stomach	0.009	0.164	0.05	0.068	0.0385	0.038	
Large Int. Sup	0.007	0.16	0.049	0.068	0.0375	0.037	
Heart	0.007	0.157	0.048	0.064	0.0355	0.036	
Kidneys	**0.081**	**2.368**	**1.163**	**1.525**	**0.803**	**0.803**	**1.625±0.576[b]**
Liver	**0.006**	**0.157**	**0.048**	**0.065**	**0.0355**	**0.036**	
Lungs	0.007	0.155	0.047	0.063	0.035	0.035	
Muscle	0.006	0.154	0.047	0.065	0.0355	0.036	
Ovaries	0.007	0.162	0.051	0.073	0.04	0.04	
Pancreas	0.011	0.172	0.053	0.071	0.041	0.041	
Bone marrow	**0.008**	**0.188**	**0.057**	**0.078**	**0.043**	**0.043**	
Superior bone	0.007	0.161	0.049	0.067	0.037	0.037	
Skin	0.006	0.148	0.045	0.061	0.0335	0.033	
Spleen	**1.735**	**4.529**	**1.402**	**1.884**	**1.8095**	**1.81**	**1.300±0.212[b]**
Testicles	0.006	0.154	0.048	0.068	0.037	0.037	
Thymus	0.006	0.154	0.047	0.063	0.0345	0.035	
Thyroid	0.006	0.154	0.047	0.063	0.0345	0.034	
Bladder	0.144	1.751	1.261	3.438	1.791	1.791	
Uterus	0.007	0.168	0.055	0.085	0.046	0.046	
Whole body	**0.011**	**0.175**	**0.056**	**0.078**	**0.0445**	**0.045**	**0.0775±0.008[b]**

† $\dot{D} = \frac{[(D(0\rightarrow3{,}25)+D(3{,}25\rightarrow68{,}25)]}{2}$

‡ $\dot{D} = \frac{[(D(0\rightarrow3{,}25)+D(3{,}25\rightarrow20{,}25)+D(20{,}25\rightarrow68{,}25)]}{3}$

[a] This work. (In gray) selected results for comparison. (In bold) the only organs evaluate by [b]Wehrmann et al.[5].

4. CONCLUSIONS

As averaged absorbed dose estimated for the two Phases (1 and 2) together, column 4 (in gray, Table 2) results is about the same values given in the column 6 (taking into account all the five phases), it is possible conclude that the curve of biodistribution splitting in two phases is sufficient to estimate dose due to LUTATE in patients.

The advantage of the proposed model is the compartimental method quickness and power to estimate dose in organs and tissues, including tumor that, in the most part, were not discriminate by voxels or phantoms built using CT images.

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