Comparasion of blood residues effects in body tissues considering dose estimation three Lutetium models

M. F. Lima[1], E. B. Araújo and C. H. de Mesquita
Instituto de Pesquisas Energéticas e Nucleares (IPEN-CNEN/SP)
Av. Lineu Prestes, 2242, Cidade Universitária - CEP 05508-000 - São Paulo – Brasil
mflima@ipen.br[1]

ABSTRACT

The lutetium biokinetic models for the estimative of the patient dose are described in the ICRP 30 and ICRP 78 reports. However, none of those models subtract the blood contained in the organ and that circulating in the organ neighborhood of the organ. Alternatively, the biokinetic data can be obtained by 'post-mortis' measurements of the radioactivity in the organs. However, this kind of sample is appropriated only for studies in animals; however, is not completely possible to avoid of the problem trying to remove all the blood on the organs. The present work is based on the Lanthanide model described in the ICRP 30, the Cerium model described in the ICRP 88 and the free Lutetium biokinectic experimental data presented by Jiménez. The MIRD protocol inside the **AnaComp™** software was used to calculate the transport of the element from fluids to other tissues and its elimination constant rate. The compartmental analysis theory helps to elucidate the dose overestimation due to the blood residues in the organs studies and to compare theoretical and experimental results. Firstly, hypothetical values of 0%, 5% and 10% of blood contained in the liver, bone and kidneys were chosen to generate the concentration response curves. Afterwards, these curves are used in the dose calculation, by interpolation of the dose in the tissues applying the reference values described in the ICRP 89 for regional blood contents in the bone (4%), liver (10%) and kidney (2%). Afterwards, a mamillar model was proposed to elucidate the data presented by Jiménez work. These results show that the three models present different results in absorbed doses. The expected doses using The ICRP models to the whole body are between 1.67 (ICRP 30) and 2.55 (ICRP 88) times the values obtained using Jiménez experimental data. The better agreement between ICRP models and experimental data was to the S*keleton:* 13.84→17.07 mGy/MBq (ICRP 88:) and (marrow +bone): 14.16mGy/MBq (Jiménez), to the *liver:* 0.36→0.43 mGy/MBq (ICRP 30) and 0.62mGy/MBq (Jiménez) and to the *kidneys*: 20 times higher (ICRP 30) and between 4 and 1000 times higher (ICRP 88) than 0.0103mGy/MBq (Jiménez). These results show that general biokinetic models for Lutetium based in other chemical elements as suggested by ICRP 30 and ICRP 88 do not reflect the real radionuclide metabolic pathways. Consequently, the choice of representative tracers and modeling methods has to be priority in the biodistribution and dosimetric studies to approval new radiopharmaceuticals.

KEYWORDS: Biokinetic model, Compartimental analysis, MIRD protocol, Dose estimation, Lutetium.

1. Introduction

For the Lanthanides, the kinetic parameters described in ICRP (30 and 88) were defined only for the generic dosimetric model, that means, without the commitment with the physiologic aspects.[1, 2 and 3]

Recently one study of internal dosimetry of radiopharmaceuticals labeled with free ^{177}Lu published by Jiménez and coworkers come up with experimental data from biodistribution and dosimetry of ^{177}Lu in mice projected directly to the human. [4 and 6]

This study is an important contribution to the ^{177}Lu biokinetics modeling because any radiopharmaceutical contained ^{177}Lu were included in the ICRP 80 Publication (International Commission on Radiological Protection), *Radiation dose to patients from radiopharmaceuticals*. [5]

The proposal of the present work is to compare the dose for ^{177}Lu calculated from models described in ICRP numbers 30 and 88 against a model, here proposed, developed in consistency with the data described by Jiménez and col. In this model, it was introduced two compartments for the bones represented by the bone marrow or the first superficial bone layer and the mineral bone.

All the data were modeled using the compartmental analysis code **AnaComp™** developed by one of the authors. [7]

2. 2. Methodology

2.1. ICRP 30 model

Biokinetics data to dose calculation, due to oral intake of Lanthanide model, presented in the ICRP30] show generic retention times (0.25 days = 2.772d^{-1}), where only the transferred fractions to destination compartment are specifically described [2].

2.1. ICRP 88 model

Biokinetics data for dose calculation due to blood injection of Lutetium uses Cerium model presented in the ICRP88 [3]. The Cerium biological half life is 3,500days (elimination from blood to excreta).

The transfer constant is:

$$k_{i,j} = \frac{\ln 2}{T_{½}b} R_j \qquad (1)$$

Where;

$k_{i,j}$ Transfer constant from original compartment *(i)* to destination compartment *(j)*;
$T_{1/2}b$ Biological half-life of chemical element (Lu) to human;
R_j Fraction of the initial injection transferred to destination compartment *(j)*.

Fig. 1 is an outline presentation of the four compartments model employed in this work. This model is supported by data from Tab. 1 and shows one same compartmental analysis scheme applicable to two models: Lanthanide group (ICRP 30) and Cerium (ICRP 88). The 4th compartment comprises the kidneys (ICRP 30) or other tissues (ICRP 88).

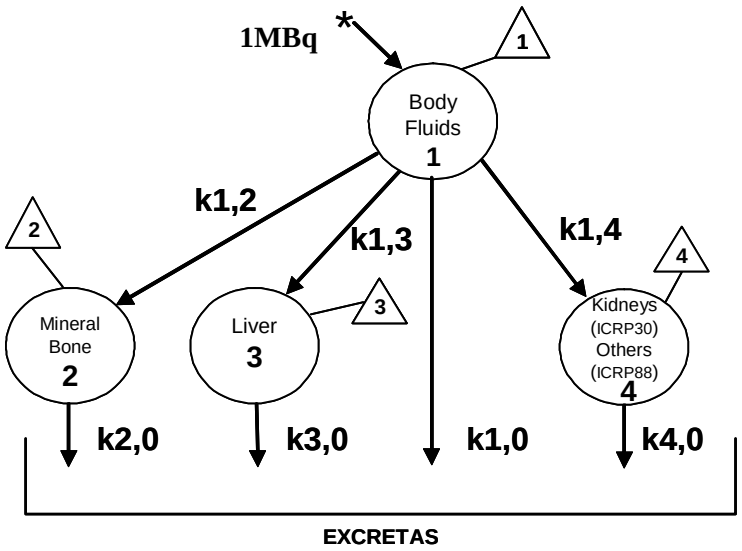

Figure. 1. Generic dosimetric compartmental model applicable to Lanthanides group according to ICRP 30 and Cerium ICRP 88.

Where:
* ↘ 1MBq injection de ^{177}Lu in the blood (time=0).
△ - Samplings.
k1,2- Transfer constant from blood to mineral bone.
k1,3- Transfer constant from blood to liver.
k1,4- Transfer constant from blood to kidneys (ICRP 30) ; blood-other tissues (ICRP 88).
k1,0- Removal constant from blood to excreta.
k2,0- Removal constant from bone to excreta.
k3,0- Removal Constant from liver to excreta.
k4,0- Removal Constant from kidneys to excreta.(ICRP 30); to other tissues-excreta (ICRP 88).

2.2. Proposed model

1MBq *

The model shown in Fig. 2 was developed to fit the data described by Jiménez and col. It considers the Lutetium that returns from the tissues to the body fluids removed by the blood stream. The phenomenon is remarkable only to some organs which was representative in terms of radioactivity concentration.

Jiménez experimental data projected directly from mice to the human was employed to feed the input data to **AnaComp** code.

2.2. AnaComp™ code data feeding

The code **AnaComp** [7] could be employed in different types of studies and it was firstly designed for metabolic studies. In dose calculations organs and tissues, **AnaComp** uses the radionuclides data from **MIRD** protocol and it is capable to calculate the doses for seven human beings phantom models, from of the newly born to adults. The **MIRD** protocol inside in the **AnaComp** routines considers the whole body more 24 organs. and tissues when calculate **AnaComp** the absorbed and effective dose to the model.

Tab. 1 gives the original values used in calculation following ICRP 30 and ICRP 88 and the experimental Jiménez data used to feed the **AnaComp** code for the dose estimate in organs and tissues according to model shown in Fig. 2. [1, 3, and 5]

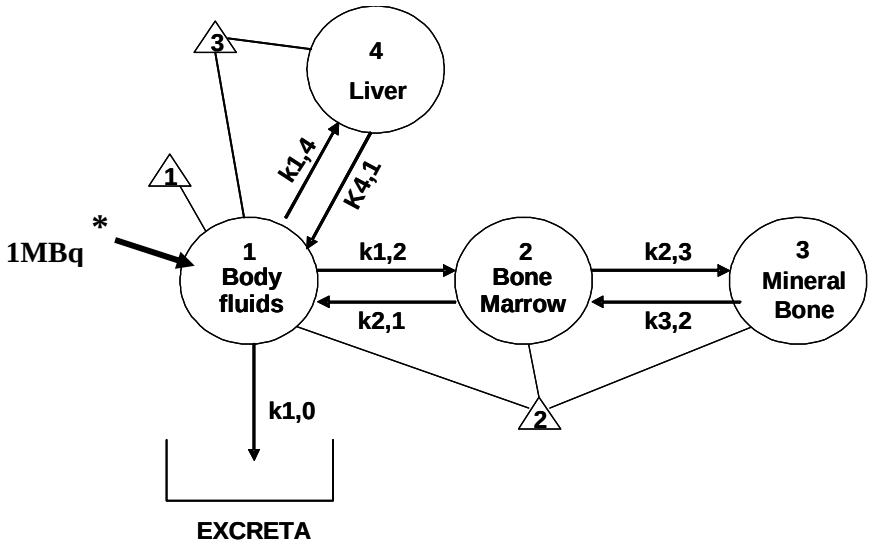

Figure. 2. Mamillar compartmental analysis scheme to Jiménez data

Where:
*↘ 1MBq injection de ^{177}Lu in the blood (time=0).
△ - Samplings,
k1,2- Transfer constant from blood to bone marrow.
k1,4- Transfer constant from blood to liver.
k1,0- Removal constant from body fluids to excreta.
k2,1- Transfer constant from bone marrow to body fluids.
k2,3- Transfer constant from bone marrow to mineral bone.
k3,2- Transfer constant from Mineral bone to bone marrow.
k4,1- Transfer constant liver to blood.

Table 1. Transfer fractions of Lutetium in the whole body

Transfer Constant Between Compartments (Original→Destination) (days^{-1})		***Transferred Fractions***		***Transferred Fractions by Time (days^{-1})***	
ICRP 30	**ICRP 88**	**ICRP 30**	**ICRP 88**	**ICRP 30**	**ICRP 88**
2.772	2.772	0.6 (blood)	0.3 (blood)	k1,2=1.632	k1,2=0.8316
		0.02 (liver)	0.5 (liver)	k1,3=0.05544	k1,3=1.386
		0.05 (kidneys)	*NA*	k1,4=0.1386	*NA*
		0.33	0.2 (other tissues)	*NA*	k1,4=0.915

NA …not available in the publications

Afterwards, in the second step of the code feed, the **AnaComp** is fed with hypotheses considering different levels of blood residues in the ex vivo sample preparation.

2.2. Modeling with hypothetical values of residual blood in the organs

The hypothetical values, after ex vivo samples washing, of 0%, 5% and 10% blood residues in the organs (mineral bone, liver and kidneys) were chosen to generate the following dose response curves from ICRP 30 and Jiménez data and after washing values of 0%, 5% and 10% blood residues in the tissues and organ (skeleton, liver and other tissues) to generate the following dose response curves from ICRP 88. [1 and 2]

Afterwards, polynomial interpolation of these curves are used to calculate the dose in the tissues applying the reference values for regional blood volumes and flow rates in adults from the ICRP 89 in the mineral bone (4%), total skeleton (7%), liver (10%), kidneys (2%).[8]

The following equations describe the dose fraction contribution of the residual blood in the organs according ICRP 30, ICRP 88 models. (2) in the mineral bone, (3) in the skeleton, (4.1 and 4.2) in the liver, (5.1 and 5.2) in the kidneys.

Skeleton:

$y = 1.071E^{-3}x^2 + 0.0115x + 27.873$ **(ICRP 30)** (2)

$y = 2E^{-5}x^2 + 0.323x + 13.838$ **(ICRP 88)** (3)

Liver:

$y = 1.14E^{-5}x^2 + 0.061x + 0.363$ **(ICRP 30)** (4.1)

$y = 1E^{-4}x^2 + 0.087x + 8.576$ **(ICRP 88)** (4.2)

Kidneys:

$y = 8.8E^{-6}x^2 + 0.026x + 0.234$ **(ICRP 30)** (5.1)

$y = 2.73E^{-1}x^2 + 0.273x + 0.041$ **(ICRP 88)** (5.2)

In this work, the proposed model considers that the entire blood fraction described in the ICRP 89 Publication remains in the dissected organs after the washing (3% in the bone, 4% in the bone marrow and 10% in the liver). The equations (6.1, 6.2, 6.3 and 6.4) created by **AnaComp** describe the ^{177}Lu biodistribution in the blood, bone marrow, cortical bone and liver, respectively.

Blood:

$$f_1 = 99.12E^{-3.18t} + 0.585E^{-1.105t} + 0.138E^{-2.58D^{-3t}} + 0.152E^{-0.029t} \quad (6.1)$$

Cortical bone:

$$f_2 = 65.49E^{-3.18t} + 52.58E^{-1.105t} + 15.37E^{-2.58D^{-3t}} - 2.46E^{-0.029t} \quad (6.2)$$

Liver:

$$f_3 = 18.21E^{-3.18t} + 52.28E^{-1.105t} + 41.34E^{-2.58D^{-3t}} - 7.27E^{-0.029t} \quad (6.3)$$

Kidneys:

$$f_4 = 17.39E^{-3.18t} - 0.301E^{-1.105t} + 2.37E^{-2.58D^{-3t}} + 15.32E^{-0.029t} \quad (6.4)$$

3. Results

Tab. 2 shows data given from **AnaComp** simulations of Lutetium concentration in organs and tissues as a function of post injection time in the blood stream following ICRP 30 and ICRP 88 models and Jiménez experimental data.

Table 2. AnaComp simulations of Lutetium concentrations in organs and tissues as a time function following ICRP 30, ICRP 88 models and Jiménez data.

ICRP 30					JIMÉNEZ				ICRP 88				
Time (days)	**Body Fluids (Blood)**	**Mineral Bone***	**Liver**	**Kidneys**	**Time (days)**	**Body Fluids (Blood)**	**Skeleton ****	**Liver**	**Time (days)**	**Body Fluids**	**Skeleton ****	**Liver**	**Other Tissues**
	100%	**0%**	**0%**	**0%**		**100%**	**0%**	**0%**		**100%**	**0%**	**0%**	**0%**
0	100	0	0	0	0	100	3	10	0	100	0	0	0
0.01	97.267	1.640	0.055	0.01	0.0833	2.1796	38.6345	16.7968	0.01	97.267	0.822	1.367	0.547
0.05	87.057	7.765	0.259	0.065	1	1.023	42.4011	9.8436	0.1	75.790	7.263	12.105	4.842
0.1	75.790	14.526	0.485	0.120	7	0.0264	32.1194	1.6601	1	6.254	28.120	46.867	18.747
0.5	25.007	44.99	1.45	0.367	14	0.00995	20.8636	1.004	10	0	29.943	49.904	19.962
1	6.254	56.24	1.874	0.446					100	0	29.412	49.020	19.608
3	0.024	59.954	1.998	0.416					500	0	27.166	45.277	18.111
7	0	59.921	1.997	0.316					1000	0	24.599	40.997	16.399
20	0	59.767	1.992	0.128					2000	0	20.168	33.613	13.445
60	0	59.295	1.976	0.008					4000	0	13.557	22.595	9.038
100	0	58.827	1.961	0					8000	0	6.126	10.210	4.084
									10000	0	4.118	6.863	2.745

***Cortical and trabecular bones.**
****Cortical and trabecular bones, red marrow and other skeleton parts.**

Tab. 3 shows data calculated using **AnaComp** and **MIRD** protocol as absorbed doses/injected activity (mGy/MBq) due to ^{177}Lu biodistribution in the whole body, bone marrow, bone, liver and kidneys. The phantom used was the adult man of 73.7 kg.

The expected doses using the ICRP models to the whole body are between 1.67mGy/MBq (ICRP 30) and 2.55mGy/MBq (ICRP 88) times the values obtained using Jiménez experimental data.

The absorbed doses in the skeleton calculated using (ICRP 88) and Jiménez experimental data (marrow +bone) shows that Cerium model to bone is acceptable: 13.84→17.07mGy/MBq (ICRP 88) and 14.16mGy/MBq (Jiménez).

The absorbed doses in the liver calculated using (ICRP30) shows a better concordance with Jiménez: 0.36→0.43mGy/MBq (ICRP 30) and 0.62mGy/MBq (Jiménez).

The absorbed doses to the kidneys calculated using (ICRP 30) and (ICRP 88) were 20 times bigger (ICRP30) and between 4 and 1000times higher.

Table 3. Comparison of absorbed doses calculated using **AnaComp™** and **MIRD** protocol due to ^{177}Lu biodistribution in the human considering ICRP 30, ICRP 88 and Jiménez data.

Organ/Tissue	Absorbed Dose (mGy/MBq)		
	ICRP 30	ICRP 88	JIMÉNEZ
Bone marrow		13.84→17.07*	1.9361
Cortical bone	27.87→27.89		12.2556
Liver	0.36→0.43	8.58→9.44	0.62031
Kidneys	0.23→0.29	0.041→10.48	0.0103
Whole body	0.1849	0.2817	0.1106

….Skeleton

Fig. 3 is the plot of retention/elimination of Lutetium by body fluids, mineral bone, liver and kidneys, following ICRP 30 (1.1) and Jiménez (1.2) and body fluids, skeleton and other tissues following ICRP 88 (1.3) models.

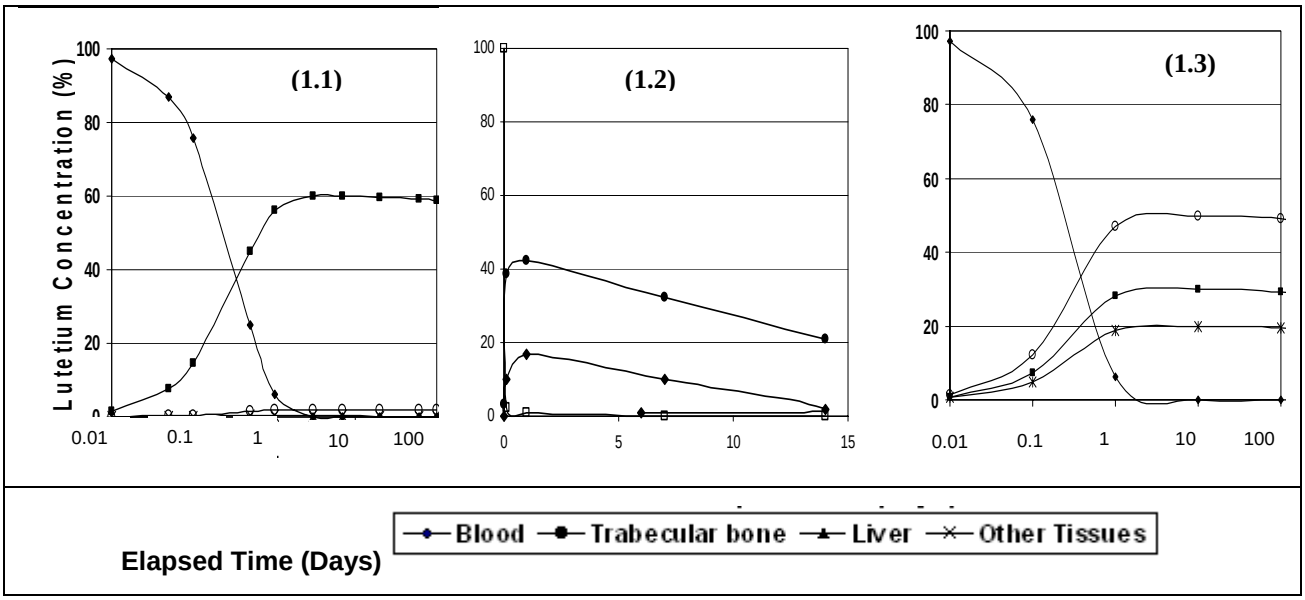

Figure 3. **AnaComp** plot of retention/elimination of Lutetium as a time function by body fluids, mineral bone, liver and kidneys, following ICRP 30 (1.1) and Jiménez (1.2) and body fluids, skeleton and other tissues following ICRP 88 (1.3) models.

4. Conclusions

Some radiopharmaceuticals labeled with beta emitters have been used on base of results obtained within gamma emitter tracers studies until more specific studies. A classical example is the ^{119}In as tracer of the ^{90}Y. [9]

On base of results presented in this work, the general biokinetic models for Lutetium based in other chemical elements as suggested by ICRP 30 and ICRP 88 do not reflects the real radionuclide metabolic paths.

Consequently, the choice of representative tracers and modeling methods has to be priority in the biodistribution and dosimetric studies to approval new radiopharmaceuticals.

Ackonowledgments: The authors gratefully acknowledge Dr. A. M. Rojo, Dr. G. M. Deluca, Dr. J. Crudo and Lic. Y.V. Jiménez for sharing the raw data modeled in this work.

REFERENCES

[1] LIMA, M. F., E. B. ARAUJO, C. H. MESQUITA, Efeito do Resíduo de Sangue nos Órgãos e sua Repercussão na Estimativa de Dose, DOSIMN 2008, Recife (2008).
[2]INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Limits for intakes of radionuclides by workers, Publication 30, Part 3, Pergamon, New York (1989).
[3] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Doses to the embryo and fetus from intakes of radionuclides by mother, Publication 88, Elsevier, Oxford (2001)
[4] JIMENEZ,Y.V., A. M. ROJO , DELUCA, G.M., CRUDO, J. Biokinetic study of free ^{177}Lu in NIH mice, DOSIMN 2008, Recife (2008).
[5] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Radiation dose to patients from radiopharmaceuticals, Publication 80, Pergamon, Oxford (1999). Addendum 2 to ICRP Publication 53.
[6] JIMENEZ,Y.V., Dosimetria interna de radiofarmacos marcados con ^{177}Lu, Instituto Balsero, Comision Nacional de Energia Atomica, Universidad de Cuyo, Buenos Aires (2007).
[7] AnaComp^{TM}, Manual do Programa AnaComp, v. 4.0, 1996.
[8] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Basic anatomical and physiological data for use in radiological protection, Publication 89. Annals of the ICRP, 32, No. 3-4, Pergamon, Oxford (2002).
[9] PAUWELS, S., Practical Dosimetry of Peptide Receptor Radionuclide Therapy with ^{90}Y-Labeled Somatostatin Analogs, 15th IRIST Meeting, Rotterdam (2002).