Internal dose assessment of ^{177}Lu-DOTA-SP for quantification of arginine renal protection effect

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ABSTRACT

^{177}Lu-DOTA-Substance P (SP) is presently investigated worldwide, in Argentina the trial is coordinated in the frame of an IAEA Contract Research Project (2011-2014).This radiopharmaceutical is proposed as potential alternative in the therapy of malignant glioblastoma.

With the aim to complete the preclinical animal studies, the biodistribution studies were carried out in normal NIH mice, for two conditions, with and without prior administration of arginine as a potential renal protective agent. These results include, in the two cases, the ^{177}Lu-DOTA-SP biodistribution analysis, the absorbed dose calculated in organs of interest and the extrapolation of the results to humans. Absorbed dose estimated in humans allowed the organs radiological toxicity assessment associated with this procedure.

The comparison of absorbed dose results between organs showed that kidney has the highest absorbed dose. Then, it is the healthy organ with the highest radiological risk, following the radiopharmaceutical intravenously administration. Based on these extrapolations, it was found that the administration of arginine prior to injection of ^{177}Lu-DOTA-SP optimize the treatment, showing a rapid clearance from the body and less retention in kidney with respect to the situation in which the amino acid is not administered.

Finally, again on the basis of extrapolations, the treatment with ^{177}Lu-DOTA-SP with pre-administration of arginine is likely to be safe in people if injected activities do not exceed the values reported in this work.

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1. INTRODUCTION

DOTA-Substance P (DOTA-SP) labeled with ^{177}Lu high specific activity is investigated as potential alternative in peptide receptor radionuclide therapy (PRRT) for treatment of malignant glioblastoma. The limiting factor in this type of therapy is the dose delivered to healthy organs therefore, it is necessary to identify the organ with the highest radiological risk and calculate the maximum activity that can be administered to a patient in a safe way; it means Maximum Tolerate Activity (MTA). Because in PRRT, the healthy organ with the highest risk of reaching the radiotoxicity is commonly the kidney [1], in this study the results of ^{177}Lu-DOTA-SP preclinical assays carried out in NIH mice [2] are compared and extrapolated to adult humans, for two conditions: with and without prior administration of arginine as a potential renal protective agent.

2. OBJETIVE

The aim of this work was to investigate the renal protective effect of arginine in the administration of ^{177}Lu-DOTA-SP in normal NIH mice and its extrapolation to standard adult patients.

3. METHODS

3.1 Biodistribution Study

Distribution of radioactivity was determined in a total of 28 normal adult mice NIH (~26g) after tail vein injection of labeled peptide (~1MBq). 41 μl of a salt solution of arginine 101 mg / ml were injected in eight of them, by the tail vein, 30 minutes before administration of the radiopharmaceutical. After sacrifice, selected organs (kidneys, liver, spleen, lungs, blood, stomach, intestine and femur) were removed, weighed and assayed for radioactivity, utilizing an automatic gamma counter Cobra II (Packard). Percentage of injected activity of ^{177}Lu-DOTA-SP per gram of tissue (%IA/g) was calculated at 30 minutes, 2, 6, 16 and 48h post-injection (n = 4) under normal conditions and after 30 minutes, 2 and 6 hours p.i. (n = 2, 3 and 3) to mice with prior administration of arginine. The results obtain for the mice with and without prior administration of arginine were compared in each time of measurement using a t test under the assumptions of normality and equal variances with significance level of 5%.

3.2 Dosimetric Studies

Experimental data of organ activity were fitted to curves, using Origin 6.1 software. It was calculated the area under the curves and normalized to IA in order to obtain the time-integrated

activity coefficients. Doses of mouse organs were determined using MIRD methodology [3]. S factor values were based on values obtained by Larsson *et al* [4]. Extrapolation to humans was performed using time scaling method [3]. Doses of human organs were calculated using OLINDA program [5] for two models: adult male (76.7 kg) and adult female (56.9 kg). It was estimated the maximum activity of ^{177}Lu-DOTA-SP that can be administered to a reference patient, without exceeding the maximum tolerance of the healthy organ with the highest radiological risk, using the expression 1:

$$Maximum\,Tolerated\ Activity\left(\frac{MBq}{Kg}\right)=\frac{Tolerance\,Dose\left(mGy\right)}{Dose\,Coefficien\,ts\,(mGy/MBq)\times mass^{TB}} \qquad (1)$$

Where the Tolerance Dose is the dose level with a probability of 5% to yield complication within five years from treatment [6] and the Dose Coefficient represents the dose in the organ per unit administered activity. The mass^{TB} takes the value of total body mass of the models used.

4. RESULTS AND DISCUSSION

Biodistribution data for both conditions are showed in Figure 1.

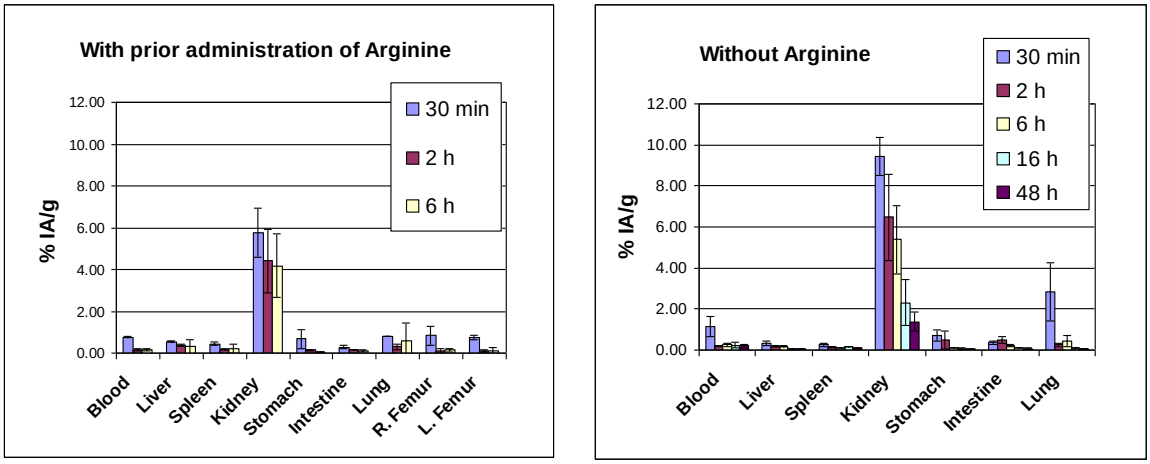

Figure 1. Biodistribution data of ^{177}Lu-DOTA-SP in normal NIH mice with (left) and without prior administration of arginine (right).

The kidney is the organ that has the highest retention of the radiopharmaceutical in the two situations, however, it is evidenced that retention in the kidney is less in the case of prior administration of arginine. For t = 30 minutes and t = 2 hours the average for the untreated group was significantly higher than the average for the group treated with arginine with a

confidence level of 95%. However, for t = 6 hours is not possible to detect differences significantly between the two groups.

Estimated radiation doses for both cases are presented in Table 1.

Table 1: Absorbed dose from ^{177}Lu-DOTA-SP per unit of IA for two conditions, with and without prior administration of arginine, in organs of the NIH mouse, adult male and adult female.

Organs	**Absorbed Dose (mGy/MBq)**					
	with Arginine			**without Arginine**		
	Mouse	Woman	Man	Mouse	Woman	Man
Kidneys	115.07	1.04	1.16	139.9	1.15	1.59
Liver	8.47	0.06	0.06	4.61	0.02	0.03
Lungs	17.05	0.02	0.02	14.57	0.06	0.05
Stomach	5.64	0.01	0.01	9.67	0.05	0.05
Spleen	27.70	0.09	0.07	14.85	0.05	0.05
Intestine	1.81	0.10	0.10	4.66	0.22	0.22
Bone Marrow	0.57	0.01	0.01	0.51	0.01	0.01

Dosimetric calculations showed that kidneys received the highest dose, for both situations, however, the dose in the kidneys is found to be lower in the case of prior administration of arginine.

On the basis of extrapolations, the maximum activity of ^{177}Lu-DOTA-SP that can be administered to patients without exceeding the tolerance dose of the kidneys (20 Gy) are presented in Table 2.

Table 2: Maximum tolerated activity (MTA) of ^{177}Lu-DOTA-SP in adult humans for two conditions: with arginine (left) and without arginine (right)

MTA for case with Arginine		**MTA for case without Arginine**	
Woman (MBq/kg)	Man (MBq/kg)	Woman (MBq/kg)	Man (MBq/kg)
338	234	306	170

It is observed that prior administration of arginine to injection of ^{177}Lu-DOTA-SP enables increasing the amount of activity administered to the patient and makes it possible to deliver a higher dose to tumor in case it is needed to control it.

5. CONCLUSIONS

The kidney is the healthy organ with the highest radiological risk, following the intravenously administration of ^{177}Lu-DOTA-SP.

It was found out that the administration of arginine prior to injection of ^{177}Lu-DOTA-SP optimize the treatment, showing a rapid clearance from the body and less retention in kidney with respect to the situation in which the amino acid is not administered.

The dosimetric results extrapolated to humans should be taken into account for not exceeding the radiotoxicological threshold in kidney and thus ensure the radiological protection of patients.

6. ACKNOWLEDGEMENTS

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7. REFERENCES

[1] M. Cremonesi, M. Ferrari, L. Bodei, G. Tosi and G.Paganelli, *The Journal of Nuclear Medicine.* **47** : 1467–1475 (2006)

[2] J.L. Crudo, A.M. Zapata, N.N. Nevares, A.C. López Bularte, J.H. Perez, A.N Zaretzky. *Alasbimn Journal* **14**, (54), Radiopharmacy section, Abstract 31 (2011)

[3] M. G. Stabin. *Fundamentals of Nuclear Medicine Dosimetry*. (New York, Springer) 2008; pp 237

[4] E. Larsson, S. Strand, M. Ljungberg and B. Jönsson. *Cancer Biotherapy & Radiopharmaceuticals*. **22**: 438-442 (2007)

[5] OLINDA-EXM Radiation Dose Assessment Software Application (FDA Approved). Vanderbilt University.

[6] B. Emami, J. Lyman, A. Brown, L. Coia, M. Goitein, J. E. Munzenrider et al. *Int. J. Radiation Oncology Biol. Phys.* **21**: 109-122 (1991)