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KEYWORDS: ^{177}Lu, Substance P, minigastrin, dosimetric studies.

ABSTRACT

DOTA-Substance P (SP) and DOTA-minigastrin (His2-MG) labeled with ^{177}Lu could be used in peptide receptor radionuclide therapy (PRRT) for treatment of various tumour species. Biodistribution studies of both radiopharmaceuticals in normal mice were performed at different times. Absorbed doses in mouse organs were estimated and extrapolated to humans. Dosimetric calculations showed that kidneys received the highest dose, for both radiopharmaceuticals. Maximum tolerated activity (MTA) of ^{177}Lu-DOTA-SP that can be administered without kidney toxicity are 414 and 422 MBq/kg for standard adult man and woman, respectively. In the same way, the MTA of ^{177}Lu-DOTA-His2-MG are 488 and 518 MBq/kg for standard adult man and woman, respectively.

INTRODUCTION

Substance P and minigastrin labeled with ^{177}Lu could be used in PRRT for treatment of glioma and medullar thyroid cancer, respectively. The aim of this work was to compare preclinical assays results of ^{177}Lu-DOTA-SP and ^{177}Lu- DOTA-His2-MG.

EXPERIMENTAL

Biodistribution Studies

Distribution of radioactivity was determined in a total of 40 normal adult mice NIH (25g) after tail vein injection of labeled peptide (~1MBq). After sacrifice, selected organs were removed, weighed and assayed for radioactivity, utilizing an automatic gamma counter. Percentage of injected activity (IA) per gram of tissue was calculated for ^{177}Lu-DOTA-SP at 30 min, 2, 6, 16 and 48h post-injection (n=6) and for ^{177}Lu-DOTA-His2-MG at 15min, 30min, 1h and 4h p.i (n=4).

Dosimetric Studies

Experimental data of organ activity were fitted to curves, using Origin 6.1 software. It was calculated the area under curves and normalized to IA in order to obtain the residence times. Doses of mouse organs were determined using MIRD methodology [1].S factor values were based on values obtained by Larsson *et al* [2]. Extrapolation to humans was performed using time scaling method [1].Doses of human organs were calculated using OLINDA program for two models: adult male and adult female. MTA for both radiopharmaceuticals was calculated assuming 20 Gy is the maximum dose that kidneys can tolerate.

RESULTS AND DISCUSSION

Biodistribution data for both radiopharmaceuticals are showed in Figure 1.

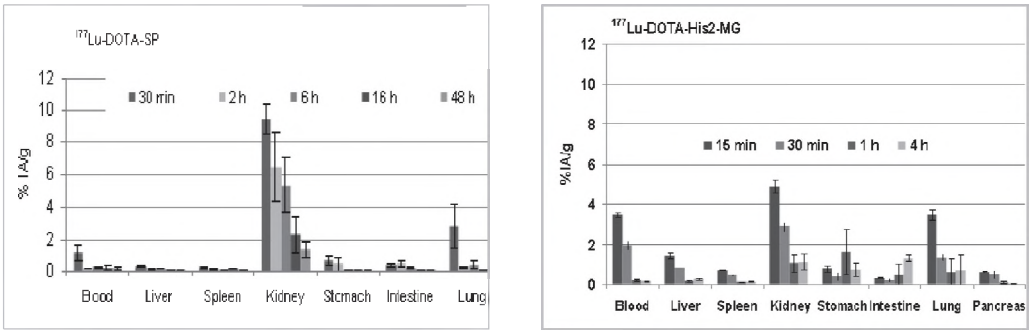

Figure 1: Biodistribution data in NIH mice for ^{177}Lu-DOTA-SP (left) and ^{177}Lu-DOTA-His2-MG (right).

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

Table 1: Absorbed dose per unit of IA for both radiopharmaceuticals in organs of the NIH mouse, adult male and adult female.

Organs	Absorbed Dose from ^{177}Lu-DOTA-SP			Absorbed Dose from ^{177}Lu-DOTA-His2-MG		
	Mouse (cGy/MBq)	Men (cGy/MBq)	Women (cGy/MBq)	Mouse (cGy/MBq)	Men (cGy/MBq)	Women (cGy/MBq)
Kidneys	14.1	0.082	0.084	15.4	0.056	0.068
Liver	0.5	0.002	0.003	3.2	0.007	0.010
Lungs	1.4	0.005	0.006	6.8	0.003	0.003
Stomach	1.1	0.005	0.005	0.8	0.011	0.011
Spleen	------	------	------	1.6	0.003	0.003

Dosimetric calculations showed that kidneys received the highest dose, for both radiopharmaceuticals. The kidney is the healthy organ at most risk. The maximum activity of both radiopharmaceuticals that can be administered to patients without exceeding the maximum tolerance of the kidneys is presented in Table 2.

Table 2: MTA for both radiopharmaceuticals in adult humans.

MTA for ^{177}Lu-DOTA-SP		MTA for ^{177}Lu-DOTA-His2-MG	
Men (MBq/kg)	Women (MBq/kg)	Men (MBq/kg)	Women (MBq/kg)
414	422	488	518

CONCLUSION

This study contributes to dosimetric preclinical stage, indicating that ^{177}Lu-DOTA-SP and ^{177}Lu- DOTA-His2-MG have a quick removal of the body and probably are safe in people if the injected activity does not exceed the values found in this study.

REFERENCES

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Biodistribution Studies: Distribution of radioactivity was determined in a total of 40 normal adult mice NIH (25g) after tail vein injection of labeled peptide (~1MBq). After sacrifice, selected organs were removed, weighed and tested for radioactivity, using an automatic gamma counter. Percentage of injected activity (IA) per gram of tissue was calculated for ^{177}Lu-DOTA-SP at 30 min, 2, 6, 16 and 48h post injection.(n=6) and for ^{177}Lu-DOTA-His2-MG at 15min, 30min, 1h and 4h p.i (n=4).

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RESULTS AND DISCUSSION

Biodistribution data for both radiopharmaceuticals are shown in figure 1 and estimated doses are listed in table 1.

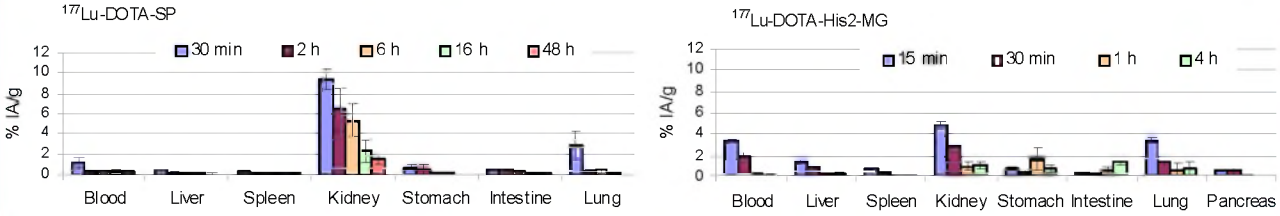

Figure 1: Biodistribution data in NIH mice for ^{177}Lu-DOTA-SP (right) and ^{177}Lu-DOTA-His2-MG (left).

Table 1: Absorbed dose per unit of IA for both radiopharmaceuticals in organs of the NIH mouse, adult male and adult female.

Organs	Absorbed Dose from ^{177}Lu-DOTA-SP			Absorbed Dose from ^{177}Lu-DOTA-His2-MG		
	Mouse (cGy/MBq)	Men (cGy/MBq)	Women (cGy/MBq)	Mouse (cGy/MBq)	Men (cGy/MBq)	Women (cGy/MBq)
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This study contributes to dosimetric preclinical stage. It shows that ^{177}Lu-DOTA-SP and ^{177}Lu- DOTA-His2-MG have a quicker elimination from the body and are probably safer for patients if the injected activity does not exceed the values found in this study.