Dosimetry of exendin-4 based radiotracer for glucagonlike peptide-1 receptor imaging: an initial report

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Abstract. Overexpression of glucagonlike peptide-1 (GLP-1) receptors in human tumours is a potential target for future imaging and therapy. The GLP-1 receptor imaging using [Lys\(^{40}\)(Ahx-HYNIC-\(^{99m}\)Tc/EDDA)NH\(_2\)]-exendin-4 could be useful in the localization of unknown insulinoma focus. The aim of this study was to present the first experience of our unit with the new radiopharmaceutical and its dose estimates. Imaging studies and dose assessment, according to the MIRD schema and MIRD Pamphlet No.11, were performed for 3 patients (2 with suspicion of insulinoma, 1 with suspected insulinoma recurrence). In the first case suspicion of insulinoma was not confirmed. In the second case localized accumulation of tracer in the pancreas was removed by surgery and the clinical symptoms of insulinoma receded. In the third case, pathological accumulation of tracer was localized and recurrence of insulinoma was confirmed in fusion with CT images. The biological half-time did not exceed 2.7 h. The effective half-time did not exceed 4.8 h. The total-body radiation dose did not exceed 0.0038 mGy/MBq and is comparable with the radiation dose to patient after somatostatin receptor scintigraphy. The highest radiation dose was calculated for kidneys (~ 0.070 mGy/MBq). [Lys\(^{40}\)(Ahx-HYNIC-\(^{99m}\)Tc/EDDA)NH\(_2\)]-exendin-4 is a good candidate for clinical GLP-1 receptor imaging studies and appears safe for the patient from radiological safety point of view.

1. Introduction

During the past two decades, peptide receptor scintigraphy with the use of somatostatin analogs (SRS, somatostatin receptor scintigraphy) has become an efficient and clinically accepted method for visualization of receptor-positive human tumours and their metastasis. But not all of the tumours overexpressed somatostatin receptors. Less than 60% of insulinomas expressed somatostatin receptor subtype 2. The sensitivity of the Octreoscan is assessed below 50% respectively [1-3].

Very high incidence and density of another regulatory peptide receptor were reported in insulinomas’ cell membrane [2]. Overexpression of glucagon-like peptide 1 (GLP-1) receptors in insulinomas may be used for effective localization of the change and consequently may result in successful surgical treatment, which is the only method for potentially relieving patients from the disease. The first tests showed that GLP-1 receptor imaging using [Lys\(^{40}\)(Ahx-DTPA,\(^{111}\)In)NH\(_2\)]-exendin-4 could be useful in the non invasive localization of insulinomas [4-5]. Compared with \(^{111}\)In-
labelled agents, examinations performed with use of $^{99m}$Tc-labelled radiopharmaceuticals are characterized by many procedural advantages related to this isotope’s physical properties. The new tracer - $[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_2]$-exendin-4, may improve the quality of images and radiation safety for patients and staff.

It is important to have information about the dose assessment from this new clinically useful new imaging option. Up to date the biokinetic characteristics and dose estimates have been reported only for animal studies.

The aim of this study is to present the first experience of our unit with this new radiopharmaceutical and our effort to establish the biokinetic characteristics of $[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_2]$-exendin-4, and to estimate the radiation dose to patients with suspicion of or confirmed insulinoma.

2. Materials and methods

2.1. Materials

Imaging studies and dose assessment were performed for 3 patients (3 females, 52 ± 6 y): (a) 48-years-old woman with hypoglycaemias, no lesion in CT and no uptake in SRS, (b) 57-years-old women with severe clinical hypoglycaemias, no lesion in CT and no uptake in SRS, and (c) 62-years-old women with malignant insulinoma after surgery with metastases to the liver in CT, with suspected recurrence and no pathological uptake in SRS. All three patients gave their written consent. The study was approved by the local Medical College Ethics Committee. The average injected activity of $[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_2]$-exendin-4 was 740 MBq.

2.2. $[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_2]$-exendin-4 preparation and radiochemical purity

Technetium-99m labeled $[\text{Lys}^{40}(\text{Ahx-HYNIC/EDDA})\text{NH}_2]$-exendin-4 was obtain from lyophilized kits prepared by the Institute of Atomic Energy, Radioisotope Center POLATOM. Exendin-4 was modified C-terminally with $\text{Lys}^{40}$-$\text{NH}_2$, where the lysine side chain was conjugated with Ahx-HYNIC (Ahx is aminohexanoic acid). Tricine and EDDA as co-ligand for $^{99m}$Tc were involved. The radiopharmaceutical procedure was carried out in the Nuclear Medicine Unit of the Endocrinology Department, Cracow University Hospital and was performed under aseptic conditions. Two-vials freeze-dried kits were used for radiolabelling with 0.3-1.5 ml of $^{99m}$Tc generator eluate (10-50mCi) followed by 20 min incubation at 80 °C. The TLC method was used for assessing the radiochemical purity of the compound.

2.3. Imaging acquisition

All images were acquired with a dual-head, large field of view E.CAM gamma camera (Siemens, 2000) with low-energy high resolution (LEHR) collimators. Whole-body scans were performed 1, 2, 3, 6, 24 and 30 h using the same procedure. The camera settings were as follows: 1024 x 256 matrix, 12 cm/min scan speed, dual-energy window for scatter correction. The standard of known activity (vial with about 10 MBq of $^{99m}$Tc) was used to obtain the imaging system calibration factor. A standard was always scanned with the patient in the same position. To obtain the transmission factor through each source region of interest (ROI), a whole-body scan of the patient was performed with identical settings and with a $^{57}$Co flood source.

2.4. Radiopharmaceutical biokinetics and dose assessment

The external conjugate view counting pair method was used for analyzing whole-body images. Firstly, ROIs were drawn visually over the source organs (kidneys, liver and lungs) on the whole body 1 h anterior scan image. These were flipped horizontally on to the posterior scan. Secondly, the ROIs were copied on to the rest of the images. The counts under the ROIs were converted to activity values after the subtraction of the background, the previously determine camera detection efficiency and attenuation correction, according to the MIRD pamphlet No. 16 equation [6-7].

All time-activity data were expressed as a percentage of the administered activity (% I.A. – the
percent injected activity). For the whole-body data the activity at $t = 0$ (100% I.A.) were estimated by fitting a mono-exponential function to the first two data points. For the source-organs, the activity at $t = 0$ was set to zero, assuming the non-instantaneous uptake in these organs.

Assuming first-order kinetics of the tracer, the area under the time-activity curve for the whole-body (the time-integrated activity coefficient), the biological half-time and the effective half-time for tracer were estimated by fitting a mono-exponential function to the data points. Areas under the time activity curves for 3 source organs (kidneys, liver and lungs) were generally estimated using the trapezoid method. A mono-exponential function was fitted to the two last data points for a better estimation of the area under the time-activity curve after the last acquired image (after 30 h).

The absorbed dose coefficient $d(r_T, T_D)$ was evaluated according to the Medical Internal Radiation Dose (MIRD) system with S values according to the MIRD Pamphlet No.11 [8-9]. The total effective dose, using weighting factors defined in ICRP Publication 103, was also evaluated [10].

3. Results

The average radiochemical purity of the administered compound, prepared according to manufacturers’ instruction and determined by TLC, was calculated to be around the 90% level.

In the first case (48-years-old woman), suspicion of insulinoma was not confirmed. In the second case (57-years-old women), accumulation of tracer in pancreas localization was remove by surgery. The postsurgical resolution of all the symptoms was observed. In the third case (62-years-old women), pathological accumulation of tracer was localized and the recurrence of insulinoma was confirmed in the CT fused image.

The percentage of the injected activity after 1 h, 6 h and 24 h in the whole-body and source organs are shown in table 1. Also in table 1 the biological half-time and the effective half-time of the tracer estimated for each patient are shown. Absorbed dose estimates are shown in table 2.

| Time (h) | Patient 1 | Patient 2 | Patient 3 |
|----------|-----------|-----------|-----------|
|          | 1         | 6         | 24        | 1         | 6         | 24        | 1         | 6         | 24        |
| Whole-body (% I.A.) | 89.3 | 36.7 | 4.0 | 87.5 | 23.6 | 2.5 | 77.7 | 25.0 | 1.6 |
| Kidneys (% I.A.) | 12.1 | 8.4 | 1.4 | 12.7 | 8.7 | 1.1 | 14.1 | 7.3 | 1.7 |
| Liver (% I.A.) | 5.3 | 2.2 | 0.2 | 4.5 | 1.7 | 0.2 | 2.8 | 0.8 | 0.1 |
| Lungs (% I.A.) | 5.8 | 1.6 | 0.1 | 4.5 | 0.9 | 0.1 | 4.5 | 0.8 | 0.1 |

B. Discussion

Imaging with GLP-1 receptor agonists is a novel option for localization of tumours overexpressing GLP-1 receptors. First clinical studies using $^{111}$In-labeled GLP-1 receptor agonist, $[\text{Lys}^{40}(\text{AhxDOTA-}^{111}\text{In})\text{NH}_{2}]$-exendin-4, revealed high sensitivity. Six out of six benign insulinomas were detected [5]. Since then, a new compound $[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_{2}]$-exendin-4 was synthesized.

In this paper the biokinetics and dose assessment of $[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_{2}]$-exendin-4 for SPECT/CT studies are presented.

$[\text{Lys}^{40}(\text{Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_{2}]$-exendin-4 showed mainly renal clearance. Activity was mainly accumulated in the kidneys, and to a lesser extends in the liver and lungs. The biological half-time did not exceed 2.7 h. The effective half-time did not exceed 4.8 h. The whole-body radiation dose did not exceed 0.0038 mGy/MBq. Table 2 shows that the highest radiation dose based on this data was estimated for the kidneys (~ 0.070 mGy/MBq). The effective dose calculated by these dose estimates did not exceed 0.0023 mSv/MBq and is comparable with the radiation dose to the patient from SRS performed with $^{99m}\text{Tc-EDDA/HYNIC-Tyr^3-octreotide}$ [11].
Table 2. Organ absorbed dose estimates in mSv/MBq for [Lys^{40}(Ahx-HYNIC-{^{99m}Tc/EDDA})NH_{2}]-exendin-4.

|                  | Patient 1 | Patient 2 | Patient 3 |
|------------------|-----------|-----------|-----------|
| Kidneys          | 0.0660    | 0.0813    | 0.0768    |
| Liver            | 0.0057    | 0.0060    | 0.0038    |
| Lungs            | 0.0049    | 0.0037    | 0.0033    |
| Spleen           | 0.0032    | 0.0039    | 0.0036    |
| Pancreas         | 0.0029    | 0.0034    | 0.0030    |
| Intestine        | 0.0042    | 0.0050    | 0.0050    |
| Red marrow       | 0.0016    | 0.0019    | 0.0017    |
| Thyroid          | 0.0001    | 0.0001    | 0.0001    |
| Muscles          | 0.0006    | 0.0007    | 0.0007    |
| Ovaries          | 0.0004    | 0.0005    | 0.0005    |
| Total Body       | 0.0038    | 0.0032    | 0.0030    |
| Effective dose   | 0.0023    | 0.0022    | 0.0021    |

Wild et al [12] evaluated the pharmacokinetics and radiation dose after injection of [Lys^{40}(Ahx-HYNIC-{^{99m}Tc/EDDA})NH_{2}]-exendin-4 in animals’ studies. For all calculations, the authors made the assumption that the Rip1Tag2 mouse biodistribution, determined as the % IA / organ, was the same as the human biodistribution. Our study showed faster retention of the tracer in human organs and the radiation dose and the effective dose to the other organs were at similar levels.

It should be emphasized that values estimated in this study are not used to evaluate the risk to a given individuals. This initial report is based on data from only 3 patients. Data from a larger number of patients is required for a complete assessment of the radiation safety of the patient. It is also necessary to take into account the blood activity and excretion concentrations. This paper provides only preliminary evaluation of organ doses from {^{99m}Tc} labeled GLP-1 receptor imaging. The data should be considered only as the basis for further evaluation of radiation safety of the radiopharmaceutical.

5. Conclusions

[Lys^{40}(Ahx-HYNIC-{^{99m}Tc/EDDA})NH_{2}]-exendin-4 is a good candidate for clinical GLP-1 receptor imaging studies and appears to be safe for the patient from a radiological safety point of view. The results provide the basis for further evaluation of the radiation safety of the radiopharmaceutical.

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