Contribution ID: **142** Type: **not specified**

Design, synthesis and evaluation of a family of 99mTc estradiol derivatives for breast cancer imaging

Tuesday, 29 October 2019 23:44 (15 minutes)

Objective:

With the objective to develop a potential radiopharmaceutical for estrogen receptors imaging we present the design of a family of 99mTc complexes derived from estradiol, using different oxidation states of the metal and chelating units and studying their influence on the overall properties of the resulting products.

Methodology:

Ligands were synthesized starting from ethinylestradiol, derivatizing the triple bond to incorporate different donor atoms to coordinate the 99mTc.
The selected labeling strategies were the formation of a Tc (I) tricarbonyl complex (C1) with an N,N,O donor atom set, a Tc (V) nitride symmetric complex (C2) with two units of estradiol and dithiocarbamate as bidentade chelator and a Tc (III) 4 + 1 complex (C3) using a ligand bearing an isonitrile moiety and an NS3 tridentate coligand. Characterization stability studies, lipophilicity, protein binding, in vitro cell binding and in vivo overall biodistribution.

Results and Discussion:

Synthesis of the ligands was successful in all cases, although the difficulty level is remarkably different.
The selected labelling strategies rendered the desired 99mTc complexes with high radiochemical purity. However, HPLC purification was required for C3.
All complexes showed high stability in labeling milieu and in human serum for at least 3 hours.
Lipophilicity expressed as log P (partition coefficient between octanol and phosphate buffer 0.1M, pH = 7.4) was 1.3 ± 0.1 for C1, 0.8 ± 0.1 for C2 and 0.48 ± 0.06 for C3. C3 exhibited the lowest lipophilicity which agrees with the bibliography that indicates that preparation of Tc(III) 4+1 complexes could be a good strategy to reduce the overall lipophilicity .
A moderate protein binding in comparison to ethynilestradiol (98%) was observed in all the three cases with values of 33 ± 11%, 41 ± 9% and 46 ± 6, respectively.
Binding to MCF7cells was 2.0 ± 0.2%, 6.8 ± 0.9% and 3,33 ± 0,12% respectively, while tritiated estradiol (Estradiol [6.7-3H (N)]) exhibited a binding of 6.6±1.4%. C2, a symmetric Tc(V)-nitrido complex bearing two units of the pharmacophore has the highest binding. Our findings are in agreement with reports that indicate the positive effect of dimerization or multimerization in receptor binding. Biodistribution in normal rats for C1 and C2 showed low blood activity (0.70 ± 0.26% and 5.13 ± 2.49% at 2 hours, respectively). However, liver uptake was very high for C1 (40.8 ± 2.4%) and moderate for C2, (13.0 ± 1.3%). Excretion occurred mainly through the hepatobiliary system with only a minor fraction excreted in the urine. C2 has the properties in vitro and in vivo properties. In vivo studies for C3 are being performed.

Conclusion:
Influence of the chelating system in the physicochemical and biological properties of Tc-labelled in biomolecules is clearly demonstrated by our experimental results. Consequently, the design of the suitable chelator is crucial in obtaining the biological stability and pharmacokinetics desired for a radiopharmaceutical.

Acknowledgments: ANII (FCE_1_2017_1_136416), CAP, PEDECIBA-Química, Bayer Schering Pharma AG, Hans-Jürgen Pietzsch.

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