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The influence of iron on the efficiency of the 68Ga labeling of DOTATOC and simple colorimetric determination of iron

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Introduction

It is well known that iron ions have a strong impact on the labeling efficiency of DOTA-peptides with 68Ga. In a draft for a monograph of 68Ga-chloride for the European Pharmacopoeia (PHARMEUROPA, Vol. 23, No. 3, July 2011) a maximum concentration for iron is given with 10 µg/GBq. The concentration should be determined by atomic absorption spectrometry.
Easier to handle but high sensitive and specific colorimetric test systems would have many advantages for clinical production of radiopharmaceuticals. Moreover, the European Pharmacopoeia describes well known methods for colorimetric determination of the total heavy metal concentration in pharmaceuticals and starting materials.
In this work we quantify the influence of iron and investigate the practical application of a colorimetric test, which is able to determine lower iron concentrations than required.

Methods

For the labeling of DOTATOC the NaCl based method (Mueller et al. , Bioconjugate Chem., 2012, 23 (8), pp 1712–1717) was used. A stock solution of iron(III) was prepared by dissolving of iron(III)-chloride in 0.1 M HCl. Different amounts of iron were added into the reaction vessels prior to the addition of 68Ga and the pH of the reaction mixtures were adjusted with sodium acetate buffer.
After heating the ratio between peptide-bound and free 68Ga was determined by radio HPLC (RP-18 column; solvent A water, solvent B acetonitrile, gradient 5-95%, 0-15 min).
The concentration of iron was cross-checked by a colorimetric test system (VWR, Microquant Iron Test, method colorimetric, Ferrospectral, 0.1- 5 mg/ml Fe).

Results

We could impressively show that the colorimetric iron test, cross-checked by a self made iron standard, safely determines the iron concentration in the reaction mixture or the eluate. The sensitivity of this test is hundred times higher than required. If 50 µg DOTATOC were used, a content of iron up to 0.6 µg shows a successful labeling but already 2 µg iron leads to an incomplete labeling. In this case the concentration of free 68Ga in the final reaction mixture is higher than 10 %. The use of 40 µg DOTATOC and 2 µg iron in the reaction mixture makes a successful labeling impossible. The concentration of 68Ga in the final reaction mixture is then higher than 90 %. After addition of 6 µg iron and the use of 50 µg DOTATOC the final concentration of free 68Ga amounts 48%. A prior concentration step with the help of a cation exchanger cartridge collects also iron(III) and it can be also eluted completely with an eluent for 68Ga-chloride. The total amount of iron in the 68Ge/68Ga generator eluate reaches therefore into the reaction mixture and would influence the labeling.

Conclusion

A content of 10 µg iron in the 68Ge/68Ga generator eluate would prevent a successful labeling of DOTA conjugated peptides. The colorimetric determination of iron is particular well suited to detect iron incorporation in the eluate or in the reaction mixture. This test system is much easier to handle than an atom absorption spectrometer in the clinical practice. Furthermore we assume that the established colorimetric test on heavy metals for pharmaceuticals and starting materials as describe in the European Pharmacopoeia would safely show toxicological concentrations on these cations.

Primary author: Dr MUELLER, Dirk (Department of Nuclear Medicine, Zentralinik Bad Berka, Germany)

Co-authors: Mr KLETTE, Ingo (Department of Nuclear Medicine, Zentralklinik Bad Berka, Germany); Dr SCHULTZ, Michael K. (Department of Radiology, The University of Iowa, Iowa City, USA); Prof. BAUM, Richard P (Department of Nuclear Medicine, Zentralklinik Bad Berka, Germany); Dr BREEMAN, Wouter A.P. (Department of Nuclear Medicine, Erasmus MC Rotterdam, The Netherlands)

Presenter: Dr MUELLER, Dirk (Department of Nuclear Medicine, Zentralinik Bad Berka, Germany)

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